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Beta Oscillations Reflect Recovery of the Paretic Upper Limb in Subacute Stroke

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Abstract

Background—Recovery of upper limb function post-stroke can be partly predicted by initial motor function, but the mechanisms underpinning these improvements have yet to be determined. Here, we sought to identify neural correlates of post-stroke recovery using longitudinal magnetoencephalography (MEG) assessments in subacute stroke survivors.

Methods—First-ever, subcortical ischemic stroke survivors with unilateral mild to moderate hand paresis were evaluated at 3, 5, and 12 weeks after stroke using a finger-lifting task in the MEG. Cortical activity patterns in the β -band (16–30 Hz) were compared with matched healthy controls.

Results—All stroke survivors ($n=22$; 17 males) had improvements in action research arm test (ARAT) and Fugl-Meyer upper extremity (FM-UE) scores between 3 and 12 weeks. At 3 weeks post-stroke the peak amplitudes of the movement-related ipsilesional β -band event-related desynchronization (β -ERD) and synchronization (β -ERS) in primary motor cortex (M1) were significantly lower than the healthy controls ($p<0.001$) and were correlated with both the FM-UE and ARAT scores ($r=0.51$ – 0.69 , $p<0.017$). The decreased β -ERS peak amplitudes were observed

both in paretic and non-paretic hand movement particularly at 3 weeks post-stroke, suggesting a generalized disinhibition status. The peak amplitudes of ipsilesional β -ERS at week 3 post-stroke correlated with the FM-UE score at 12 weeks ($r=0.54$, $p=0.03$) but no longer significant when controlling for the FM-UE score at 3 weeks post-stroke.

Conclusions—Although early β -band activity does not independently predict outcome at 3 months after stroke, it mirrors functional changes, giving a potential insight into the mechanisms underpinning recovery of motor function in subacute stroke.

Keywords

stroke; motor recovery; magnetoencephalography; beta oscillations; event-related synchronization; event-related desynchronization

Introduction

Only 40-55% of stroke survivors achieve independence in daily activities,¹ most are limited by residual limb paresis.² Two critical questions surrounding the recovery of motor behaviour post-stroke remain to be answered: (1) can outcome be accurately predicted early after stroke for an individual patient, and (2) can the mechanisms underpinning recovery be elucidated, so that we can optimize that recovery.

Function in the paretic upper limb at 3-6 months after stroke can partly be predicted using the proportional recovery rule based on the baseline Fugl-Meyer upper extremity (FM-UE) score.³⁻⁵ Although this rule has recently been questioned because of mathematical coupling between the baseline and change score,^{6,7} there is convergent evidence that the integrity of the ipsilesional corticospinal pathway early after stroke is of central importance for motor outcome,⁸ which has been used to stratify stroke survivors in terms of recovery of motor function.⁹

fMRI and PET studies have consistently demonstrated that cortical remodeling in both the ipsilesional and contralesional hemispheres¹⁰ also plays a key role in functional recovery after stroke,¹¹⁻¹⁴ especially in subacute stroke stage.¹⁵ However, fMRI and PET measure blood oxygenation level and regional blood flow, raising the potential confound of concurrent impairments of cerebrovascular reactivity and hemodynamic insufficiency.¹⁶

Magnetoencephalography (MEG) directly quantifies neural activity and therefore is unaffected by potential changes in neurovascular coupling. In addition, MEG can be used to detect activity within cortical microcircuits, which comprise reciprocal activity in both glutamatergic and GABAergic neurons and hence might be difficult to quantify using fMRI or PET. Oscillations, particularly in the β -band (16-30 Hz), reflect this reciprocal activity, and hence are sensitive to changes in the excitatory/inhibitory balance within local microcircuits, although the precise relationship remains to be elucidated. β -band activity within the primary motor cortex (M1) is of particular interest as it is known to be central to voluntary movements in humans,¹⁷ and is likely therefore to have a critical role in motor recovery. A prominent event-related desynchronization (β -ERD) occurs during movement preparation and movement, and an event-related synchronization (β -ERS) occurs after

cessation of movement,¹⁸ both of which have been shown to be specifically altered after stroke.^{19–23} The β -ERD and β -ERS reflect distinct physiological processes though both have previously been shown to be altered by changes in GABAergic signalling,^{24,25} which is central to post-stroke recovery.^{26,27}

The β -ERD starts prior to movement in the contralateral postcentral gyrus, spreading immediately to the bilateral sensorimotor cortices, and has been associated with motor preparation, execution, and imagery.^{18,28,29} Previous EEG/MEG studies have shown that the ipsilesional amplitude is reduced after stroke, and such reduction correlates with motor impairment post-stroke.^{19,20}

The β -ERS appears at the cessation of movement. The β -ERS has been suggested to reflect motor cortical deactivation, or an increase of intracortical inhibition.^{24,30–32} The role of β -ERS in motor recovery is less clear than that of β -ERD. An MEG study in chronic stroke patients reported a positive correlation between ipsilesional β -ERS and concurrent motor scores,²⁰ but another study revealed a decrease in β -ERS in bilateral M1s after 2 weeks of rehabilitation.³³ Somatosensory stimulation studies in acute stroke demonstrated decreased β -band rebound in either paretic or nonparetic hand stimulation, with subsequently increased during recovery.^{22,23,34}

However, most of these were cross-sectional studies providing inconsistent evidence influenced by the heterogeneity in stroke survivor enrolment (post-stroke time, stroke severity, mixed ischemic and haemorrhagic stroke, mixed arterial territories, mixed subcortical and cortex involvement).^{9,33,35–37}

Here, we have studied longitudinal MEG changes in a relatively homogenous cohort of first-time subcortical ischemic stroke in the middle cerebral artery territory at the week 3, 5, and 12 after stroke to test a number of hypotheses. We predicted that the amplitudes of β -ERD and β -ERS in the ipsilesional M1 would be decreased at 3 weeks post-stroke, and on a subject-by-subject basis would relate to function. Further, we hypothesized that β -ERD and β -ERS at week 3 post-stroke would correlate with functional outcome at 12 weeks post-stroke. Finally, the pattern of longitudinal β -ERD/ERS changes over bilateral hemispheres would reflect cortical plasticity during post-stroke motor recovery.

Methods

Twenty-two patients aged 20–80 with first-ever, unilateral, subcortical ischemic stroke in the middle cerebral artery (MCA) territory, with mild to moderate hand weakness (finger extensor strength 3/5 Medical Research Council grade), ensuring that the finger lifting task could be adequately performed, were recruited at 2–4 weeks after stroke onset and hospitalized at the Taipei Veterans General Hospital for 2 weeks of intensive rehabilitation which included 2 daily sessions of 90-minute physiotherapy except weekends (30 hours/10 days). The exclusion criteria included a modified Rankin Score (mRS) of 4–5, concomitant major neurological diseases or severe medical diseases. Another 25 age- and sex-matched healthy subjects were enrolled as controls. All participants in this study were right-handed as determined by Edinburgh Handedness Inventory.³⁸ Written informed consent was obtained

from each participant in advance. The study was approved by the ethics committee of the Taipei Veterans General Hospital.

Stroke survivors were followed at 3 time points: **T1**: as the baseline, at about the 3rd week after stroke, **T2**: immediately after 2 weeks of intensive rehabilitation, at about the 5th week after stroke, and **T3**: at the 12th week after stroke (followed up at an outpatient clinic). Each evaluation consisted of the FM-UE score,³⁹ the Action Research Arm Test (ARAT) score,⁴⁰ and task-related MEG (see below). The same MEG protocol was performed once in healthy controls.

Transcranial Magnetic Stimulation (TMS)

Corticospinal excitability was measured at enrolment in stroke survivors alone using single-pulse TMS generated by a Magstim Rapid² simulator (Magstim Co., Whitland, UK) applied to the ipsilesional M1 and recorded with surface electromyography (EMG) on the paretic extensor carpi radialis (ECR) muscle. The motor evoked potential (MEP) peak-to-peak amplitude was averaged from 12 successive MEPs evoked every 5 seconds for 1 minute at an intensity of 120% baseline resting motor threshold (rMT).⁴¹ Corticospinal excitability was measured by an experienced technician, at least 2-3 days before the MEG measurement.

Brain Magnetic Resonance Imaging

To produce a group lesion map, ischemic stroke lesions delineated from individual diffusion weighted images were overlaid on a standard brain template using MRIcron® software.⁴² All subjects also received 3-Tesla MRI scans (Discovery MR750, General Electric Company) to obtain high resolution 3-dimensional T1 images for MEG source co-registration. Individual MRI cortical surfaces were reconstruction by FreeSurfer software⁴³ followed by downsampling to 8,000 vertices.

MEG Acquisition

MEG was recorded in a magnetically shielded room using a whole-head array Neuromag VectorviewTM MEG system (Elekta, Helsinki, Finland) with a 500 Hz sampling rate. Only the planar gradiometer signals (204 channels) were analysed in this study.

Electrooculography (EOG) channels over the right upper and left lower orbital regions and electrocardiography (ECG) channels over bilateral arms were used to detect blink, ocular and cardiac artefacts. Surface EMG channels on bilateral extensor digitorum communis muscles were used to monitor motor task performance. The EMG signals were processed with 20 Hz high-pass filtered then rectified to determine the duration of EMG activity following the methods in previous literature.⁴⁴

The MEG paradigm comprised a self-paced unilateral index finger lifting task every 7 seconds, for both sides consecutively. A total of 100 trials for each side were collected with a short break after the first 50 trials (total about 20 minutes). Before signal acquisition, all participants were instructed to perform steady finger lifting (20-40 degrees) while relaxing other parts of the body. The movement onset of finger lifting was detected by an optic detection pad.

MEG Analysis

MEG data were analysed using Brainstorm software.⁴⁵ The continuous MEG raw data were epoched into the -3 to 3 second segments relative to movement onset. Epochs were discarded if visual inspection revealed noisy segments, concurrent EOG signals were larger than 200 microvolt (μV), or MEG signals were larger than 4000 femtotesla (fT). EOG and ECG artefacts were removed by signal-space projectors built in Brainstorm software. MEG artefact-free data was filtered into the β -band (16-30 Hz), squared and averaged to yield β -band specific power, then projected into individual MRI cortical surface by minimum norm estimate (MNE), and normalized to the Colin27 template cortex. Event-related desynchronization and synchronization (ERD/S) were quantified by calculating frequency-specific power change relative to reference period (-3~-2 seconds relative to movement onset) with the expression: $\text{ERD (or ERS) \%} = \frac{A-R}{R} \times 100$ (A =the power within the frequency band of interest during the active period of the event; R = mean power of the reference period).¹⁸ The peak amplitude of ERD and ERS was determined during the period of -2~2 seconds and 0~3 seconds respectively from the maximal response vertices for each individual. In order to ensure that the findings in this study were not simply due to a slowing of β -activity in stroke survivors, we performed a fast Fourier transform from -3 to 3 seconds relative to movement onset and characterised the peak frequency. This did not differ significantly either between stroke survivors and controls [$t(45)=-.030$, $p=0.76$] or across time in the stroke survivors [$F(2,20)=3.04$, $p=0.071$] (Supplementary Table S1).

Statistical Analysis

All analyses were performed using the SPSS software (version 15.0, Chicago, IL, USA). When comparing demographic characteristics between the stroke and control groups, chi-square tests were used for categorical data and Mann-Whiney U tests were used for continuous data. Multivariate analysis of variance (ANOVA)s were performed to compare the difference between control and stroke groups in the ERD/S parameters (amplitude) and EMG parameters (duration). One-way repeated measures ANOVAs were performed to evaluate the changes over time in motor scores, electrophysiological measurements and ERD/S parameters among the 3 post-stroke time points, followed by *post-hoc* t-test with Bonferroni correction. The relationship between motor scores and MEG parameters was examined using Spearman's rank correlation to minimize the ceiling effects of maximum motor scores. To validate any association of MEG parameters with motor outcomes at T3, a partial correlation analysis controlling motor scores at T1 was performed.

Results

A total of 22 (17 males) stroke survivors and 25 age- and sex-matched healthy controls were enrolled in this study (Table 1). Stroke survivors had a median age of 60 years (55-62), were a median of 21 days (16-25) after stroke onset, with median NIHSS, 3 (2-4); ARAT, 36 (18-54); FM-UE, 51 (43-60) at enrolment, belonging to mild to moderate stroke severity. Twelve stroke survivors had right hemispheric stroke. The group lesion map (Fig. 1) showed overlapped infarctions in the corona radiata and basal ganglia within the middle cerebral artery territory without cortical involvement. The infarction size (mean \pm standard error) was $2.53\pm 0.43 \text{ cm}^2$ (range:0.55~8.4 cm^2). All our stroke survivors had a quantifiable MEP at

enrollment, with median MEP amplitude at 120% baseline rMT of 0.172mV (range 0.10-0.26).

Twenty-two stroke survivors took part at T1. Of these, data from 15 stroke survivors was recorded at T2, and 16 at T3. Three stroke survivors were excluded from T2 and T3 as they did not undertake hospitalization rehabilitation after the T1 evaluation. Four stroke survivors at T2 and 3 at T3 declined follow-up.

Stroke survivors showed significant functional improvements between week 3 and week 12

As would be expected, stroke survivors' behaviour improved after stroke. Both the FM-UE and ARAT scores showed significant increases after 2 weeks of rehabilitation (T2) and at 3 months after stroke (T3) compared with baseline (T1) [FM-UE: $F(1.25, 13.74)=25.13$, $p<0.0005$; ARAT: $F(2, 22)=21.92$, $p<0.0005$; Fig. 2A-B]. Post-hoc Bonferroni-corrected paired-samples t-tests demonstrated significant differences between all 3 timepoints (FM-UE: T2-T1 $p=0.002$, T3-T1 $p=0.001$, T3-T2 $p=0.003$; ARAT: T2-T1 $p=0.002$, T3-T1 $p=0.001$, T3-T2 $p=0.019$).

It has previously been shown that behavioural measures early in stroke correlate with subsequent behavioural outcome.⁵ In line with this, the FM-UE (or ARAT) score at T1 significantly correlated with the FM-UE (or ARAT) score at T3 in our stroke cohort (FM-UE: $r=0.79$, $p<0.0005$; ARAT: $r=0.65$, $p=0.006$, Fig. 2C-D).

Stroke survivors showed an initial mildly slowing of movement, which normalised by 5 weeks post-stroke

We then went on to investigate the duration of movement in finger lifting. The surface EMG signals of the extensor digitorum communis muscle during paretic [nondominant left hand in controls] finger-lifting revealed a group difference in EMG movement duration [$F(3, 74)=3.34$, $p=0.024$]. Post-hoc t-tests with Bonferroni correction revealed that the EMG duration was significantly prolonged in stroke survivors at T1 (992 ± 151 ms) as compared with controls (594 ± 151 ms, $p=0.017$), but normalized after T2 (Fig. 2E). However, there was no significant correlation between the EMG duration and β -ERD or β -ERS peak amplitudes in either healthy controls and stroke survivors (all p 's >0.1 , Supplementary Table S2). The EMG movement duration in non-paretic [right in controls] hand finger-lifting task showed no group difference [$F(3, 68)=0.46$, $p=0.71$, Fig. 2E].

Stroke survivors showed changes in timings in β -ERD and β -ERS compared with healthy controls

We next wished to investigate the neural correlates of the paretic finger movement. Activity in the β -band at key temporal phases, including (1) motor preparation (-700 ms), (2) movement onset (0 ms), (3) maximal ERD, (4) 700 ms and (5) 900 ms postmovement and (6) maximal ERS, were shown in both controls (non-dominant, left hand, $n=25$) and right hemispheric stroke survivors (left paretic hand) at T1 ($n=12$), T2 ($n=7$), and T3 ($n=8$) (Fig. 3A). The topography threshold was set at $\pm 10\%$ across all figures to enable visual comparisons of all key phases among all groups.

At the motor preparation phase (-700 ms, with movement onset at 0 ms), stroke survivors at T1 showed early ERD activation over the contralesional premotor cortex as compared to healthy controls (arrow in Fig. 3A). During stroke recovery (T2 and T3), this contralesional early activation mostly subsided. At the postmovement phase of approximately 900 ms, stroke survivors at T1 showed prolonged ERD activation in both hemispheres (i.e., delayed appearance of ERS response, arrowhead in Fig. 3A), and such ERD prolongation was shortened to approximately 700 ms at stroke T3. The group-level ERD and ERS curves in the bilateral M1 reflected similar ERD duration changes (Fig. 3B).

β -ERD/ERS amplitudes were decreased at baseline in stroke survivors and increased during recovery

To investigate post-stroke specific changes in β -band activity, in line with our *a priori* hypotheses we went on to investigate the peak amplitudes of the β -ERD and the β -ERS between healthy controls and stroke survivors at T1 (Fig. 3C-D). The β -ERD peak amplitudes (%) of healthy controls and stroke survivors at T1, T2, T3 (Fig. 3C) were 24 ± 1.5 , 14 ± 1.8 , 16 ± 2.6 , and 19 ± 3.0 in the ipsilesional [right in healthy controls] M1, and 20 ± 1.7 , 16 ± 2.5 , 15 ± 2.8 , and 16 ± 3.2 in the contralesional [left in healthy controls] M1. The β -ERS peak amplitudes of healthy controls and stroke survivors at T1, T2, T3 (Fig. 3D) were 49 ± 5.7 , 14 ± 2.0 , 20 ± 4.0 , and 24 ± 4.4 in the ipsilesional [right in healthy controls] M1, and 34 ± 2.7 , 12 ± 1.4 , 18 ± 2.9 , and 26 ± 4.5 in the contralesional [left in healthy controls] M1. A 2×2 mixed model ANOVA was run with β -band metric (β -ERD, β -ERS) and hemisphere (ipsilesional [right for controls], contralesional [left for controls]) as within subject factors, group (control, stroke T1) as between subject factor, and peak amplitudes of β -band metric as the dependent variables. There was a significant difference between stroke survivors and controls [$F(1,45)=24.8$, $p<0.001$], as well as the main effect of metric [$F(1,45)=15.44$, $p<0.001$] but not hemisphere [$F(1,45)=2.44$, $p=0.125$]. There was also a significant metric by group interaction [$F(1,45)=5.75$, $p=0.001$], in line with our hypothesis that specific aspects of β -band activity may be differently affected at subacute stroke. *Post-hoc* testing revealed significant difference between control and stroke T1 [$t(45)=4.21$, $p<0.001$] in ipsilesional β -ERD (Fig. 3C) and between control and stroke T1 in both ipsilesional β -ERS [$t(45)=4.17$, $p<0.0005$] and contralesional β -ERS [$t(45)=3.83$, $p<0.001$; $\alpha=0.025$ (corrected for multiple comparisons); Fig. 3D].

We then went on to look at the change in these metrics during recovery. We ran a $2 \times 2 \times 3$ repeated-measures ANOVA for stroke survivors who have completed all three sessions, with hemisphere (Ipsilesional, Contralesional), β -band metric (β -ERD, β -ERS) and timepoint (T1, T2, T3) as within-subject factors. This demonstrated a main effect of time [$F(2,22)=5.39$, $p=0.012$] but no main effect of hemisphere [$F(1,11)=0.071$, $p=0.79$] or β -band metric [$F(1,11)=2.81$, $p=0.12$]. There were no significant interaction terms. *Post-hoc* testing in ipsilesional M1 β -ERD peak amplitude showed significant changes over time [$F(2,22)=3.78$, $p=0.039$; Fig. 3C-D], although Bonferroni post-hoc tests revealed only a trend of increase from T1 to T2 ($p=0.11$), and T1 to T3 ($p=0.16$). Contralesional M1 β -ERD showed no changes over time. The ipsilesional M1 β -ERS amplitude showed no changes over time [$F(2,22)=1.73$, $p=0.20$], but the contralesional M1 β -ERS amplitude significantly

changed over time [$F(1.17,12.8)=4.71$, $p=0.045$]. Bonferroni post-hoc tests revealed a significant increase from T1 to T2 ($p=0.04$); a trend of increase from T1 to T3 ($p=0.15$).

In order to determine whether these metrics were still significantly different from control at T2 or T3, we ran the same analyses that performed at T1. There was still a significant difference between controls and stroke survivors at T2 in both the ipsilesional β -ERS amplitude ($p=0.006$) and the contralateral β -ERS amplitude ($p=0.013$), but only in the ipsilesional β -ERS amplitude at T3 ($p=0.016$; Figures 3C-D).

β -ERD/ERS amplitude in stroke recovery related to motor function

We next wanted to investigate whether any of our β -band metrics were related to behaviour. We used two measures of behaviour, the FM-UE and the ARAT. The ipsilesional M1 β -ERD peak amplitudes were significantly positively correlated with both the concurrent FM-UE at stroke T1 and ARAT at stroke T1, T2, T3 ($r=0.51$, $p=0.016$ for T1 β -ERD and T1 FM-UE; $r=0.61$, $p=0.003$ for T1 β -ERD and T1 ARAT; $r=0.66$, $p=0.008$ for T2 β -ERD and T2 ARAT; $r=0.60$, $p=0.015$ for T3 β -ERD and T3 ARAT, α [adjusted for multiple comparisons (3 time points)]=0.017, Fig. 4A), such that stroke survivors with greater ipsilesional β -ERD peak amplitude had better motor function.

The ipsilesional β -ERS peak amplitudes were significantly positively correlated with concurrent FM-UE and ARAT at stroke T1 ($r=0.69$, $p<0.0005$ for T1 β -ERS and T1 FM-UE; $r=0.49$, $p=0.02$ for T1 β -ERS and T1 ARAT; α [adjusted for multiple comparisons (3 time points)] = 0.017; Fig. 4B). Contralateral β -ERD and β -ERS showed no significant functional correlations with concurrent motor scores.

Association of early β -ERD/ERS with functional outcome at 3 months

We were interested in whether outcome at 3 months (T3) correlated with either the β -ERD or β -ERS in the subacute stroke (T1). The ipsilesional β -ERD amplitude at T1 showed no significant correlation with T3 FM-UE ($r=0.27$, $p=0.31$) or T3 ARAT ($r=0.47$, $p=0.07$) partly related to ceiling effect of motor scores at T3 (Fig. 4C). As for the ipsilesional β -ERS peak amplitude at T1, it was positively correlated with T3 FM-UE ($r=0.54$, $p=0.031$, Fig. 4D).

We then wished to know whether the ipsilesional β -ERS amplitude shared common effects in correlation with the T1 FM-UE, possibly suggesting a common mechanism, or whether ipsilesional β -ERS amplitude could independently predict behavioural recovery. We performed a partial correlation analysis between ipsilesional β -ERS amplitude at T1 and FM-UE at T3, controlling for FM-UE at T1 and demonstrated that the relationship was no longer significant.

Motor task-dependent β -oscillations during non-paretic hand movement

Finally, we applied the equivalent analyses in non-paretic [right in controls] hand movement to explore if these β -ERD/ERS changes were specific to paretic hand movement or as a general post-stroke phenomenon. The MEG data of non-paretic [right in controls] hand was measured immediately after the paretic hand [left in controls] in the same MEG session, available in 19 (T1), 13(T2), and 16(T3) of our stroke survivors and in 25 controls. The

EMG duration of non-paretic hand movement after stroke showed no difference when compared to controls [right hand] or during post-stroke recovery (Fig. 2E). As disclosed in Figure 5, there was no early ERD at stroke T1, unlike in the paretic hand, but similar delayed appearance of ERS response was noted (arrowhead in Fig. 5A) when compared to controls. The ERD prolongation also shortened to approximately 700 ms at stroke T3 (Fig. 5A-B). The β -ERD peak amplitudes (%) of healthy controls and stroke survivors at T1, T2, T3 (Fig. 5C) were 17 ± 1.6 , 14 ± 1.9 , 12 ± 2.9 , and 14 ± 2.1 in the ipsilesional [right in healthy controls] M1, and 19 ± 2.3 , 18 ± 2.6 , 16 ± 2.7 , and 19 ± 2.6 in the contralesional [left in healthy controls] M1. The β -ERS peak amplitudes of healthy controls and stroke survivors at T1, T2, T3 (Fig. 5D) were 29 ± 3.9 , 17 ± 3.6 , 14 ± 3.6 , and 24 ± 4.2 in the ipsilesional [right in healthy controls] M1, and 44 ± 6.4 , 25 ± 4.7 , 23 ± 5.6 , and 26 ± 4.2 in the contralesional [left in healthy controls] M1. There was a significant decrease of β -ERS at stroke T1 and T2 [$F(1,42)=6.33$, $p=0.016$ for T1, $F(1,42)=6.50$, $p=0.015$ for T2] when compared to controls, but not in β -ERD (Full statistics in Supplementary Table S3). *Post-hoc* testing revealed a significant decrease of contralesional β -ERS [$t(42)=2.32$, $p=0.025$ for T1; $t(36)=2.35$, $p=0.024$ for T2], and a trend of decrease of ipsilesional β -ERS [$t(42)=2.16$, $p=0.037$ for T1; $t(36)=2.13$, $p=0.04$ for T2, $\alpha=0.025$ for multiple comparisons]. The peak amplitudes of β -ERD or β -ERS showed no significant difference between T1, T2, and T3 (all $p>0.1$, full statistics in Supplementary Table S3). There was no significant behavioural correlation with the β -ERD/ERS metrics of non-paretic hand movement (all $p>0.1$, Supplementary Table S4).

Discussion

We performed this study to characterize how β -band activity changed during motor recovery post-stroke. The homogenous stroke profile in our stroke survivors (mild to moderate unilateral MCA subcortical infarctions) enabled us to extract reliable information in this common clinical stroke syndrome. As expected, the motor outcome could be predicted by early motor scores at the subacute timepoint, while the neuroplastic mechanisms underlying motor recovery were reflected by MEG markers including the ipsilesional β -ERD and β -ERS peak amplitudes. Our results were in line with earlier studies by Parkkonen et al. who utilized both tactile stimulation and passive movement in acute stroke survivors with longitudinal follow-up^{22,34}.

Changes in ipsilesional, not contralesional, β -band metrics, reflect behavioural improvements

Our data demonstrate clear relationships at every time point between the ipsilateral β -ERD/ERS amplitude and both the ARAT and FM-UE. However, there were no relationships observed between β -band metrics in the contralesional hemisphere. The contralesional hemisphere was proposed to have different role at subacute and chronic stroke,^{46,47} and our findings highlighted the importance of ipsilesional hemisphere reorganization at subacute stroke. It may well be that contralesional hemisphere reorganization plays an important role later in the recovery process.

β -band metrics at T1 hint mechanisms underlying functional recovery

We showed that ipsilesional M1 β -band metrics correlated with 3-month FM-UE motor outcome, though these relationships were no longer significant when T1 FM-UE score was included. This suggests that the β -band metrics and FM-UE share common variance, as would be suggested by their relationship at each time point in the study, highlighting perhaps that β -band metrics can elucidate the mechanisms underpinning functional recovery post-stroke.

β -ERD amplitude is thought to reflect neural activation in M1

In line with previous studies,^{19,20,48} we found that the ipsilesional β -ERD peak amplitudes decreased after stroke and correlated with concurrent motor scores. In this longitudinal study, we also demonstrated that ipsilesional β -ERD peak amplitudes increased during motor recovery and correlated with behavioural improvements. The β -ERD appears to be a reflection of overall cortical excitability^{49,50} and decreased in post-stroke ipsilesional M1. A decrease in β -ERD peak amplitude in M1 also occurs in the slowing of movement in movement disorders such as Parkinson's Disease;⁵¹ leading to the suggestion that an abnormally low β -ERD peak amplitude is pathological and may lead to the decrease in the precise and tractable control of movements.⁵²

β -ERS amplitude is thought to reflect changes in intracortical inhibition in M1

After stroke, the β -ERS peak amplitudes significantly decreased in both hemispheres and remained low during stroke recovery particularly in the ipsilesional hemisphere. At stroke T3, the ipsilesional β -ERS peak amplitudes were still significantly lower than that in healthy controls (Fig. 3D).

β -ERS is thought to reflect intracortical inhibition and has been related to cortical GABA concentrations.⁵³ Therefore, decreased β -ERS peak amplitudes in acute/subacute stroke may reflect reduced intracortical inhibition, which is known to occur early after stroke.²⁶ Consistent with this, the TMS metric of Short-Interval Cortical Inhibition (SICI) has also revealed decreased intracortical inhibition in both hemispheres after acute stroke, especially in ipsilesional hemisphere.⁵⁴ Low β -ERS peak amplitudes at T1 in ipsilesional hemisphere correlated with functional outcome at T3 (Fig. 4D), suggesting that a decreased β -ERS may be beneficial role for promoting motor recovery. One previous MEG study revealed decreased β -ERS amplitudes in the bilateral M1 following 2 weeks of rehabilitation in chronic stroke survivors,³³ supporting the inference regarding low β -ERS status.

β -ERS changes in non-paretic hand movement reflect generalized disinhibition status in subacute stroke

The delay onset and decreased peak amplitude of β -ERS was observed in both paretic and non-paretic hand motor task at subacute stroke (Fig.3A&5A), although the changes were more prominent and correlated with behaviour only in paretic hand movement. Similar phenomenon was observed in the TMS study that the SICI also decreased in contralesional M1 particularly at subacute stroke^{54,55}. Parkkonen et al. also discovered the β -rebound decreased after somatosensory stimulation in both paretic and non-paretic hand when compared to healthy controls, and only the β -rebound of paretic hand correlated with

concurrent motor scores^{22,34}. Subacute stroke constitutes a unique highly sensitive period for motor recovery¹⁰, and the bi-hemispheric changes in β -ERS featured the global disinhibition status in this period.

Many factors may affect ERD and ERS responses during motor task, including the length of sustained movement⁵⁶, the number of activated muscles³², and the rate of force during isometric contraction⁵⁷. Therefore, we chose a relatively effortless simple finger lifting task in this study. The index finger lifted around 30-degree angle off the optic detection pad then back to original neutral position without sustained movements, complex or isometric muscle contractions. While we cannot rule out that the differences we observed between stroke survivors and controls in terms of the ERD and ERS were driven by changes in kinematics, no significant correlations were observed between β -ERD, β -ERS amplitude and the EMG duration (Supplementary table S2), and the non-paretic hand movement disclosed similar pattern of changes in β -ERD/ERS duration.

There are limitations in this MEG study. The ceiling effects of motor scores in the 12th (T3) weeks after stroke onset may underestimate the correlation with baseline β -ERD/ERS. The effect of handedness may exist but unlikely change out main findings because the topographical patterns and quantification results were similar in our stroke survivors with either the left (N=12) or right (N=10) paretic hand. In this study, we cannot draw definitive conclusions about the effects of intensive rehabilitation because the scores of stroke survivors at T2 were between those at T1 and T3. It is therefore not possible to disentangle the effects of intensive rehabilitation from those of the simple passage of time.

Conclusions

Our work revealed dynamic features of β -oscillations during motor recovery from subacute to chronic stage in stroke survivors with mild to moderate hand paresis. Ipsilesional β -ERD and β -ERS peak amplitudes at subacute stroke were functional MEG markers synchronized with the changes of clinical motor scores. β -ERS peak amplitudes decreased in either paretic or non-paretic hand movement at subacute stroke reflected the generalized disinhibition status. These neural features hinted the integrity of M1 activities and the maintenance of intracortical disinhibition were involved in cortical remodeling mechanisms during motor recovery, particularly at subacute stroke.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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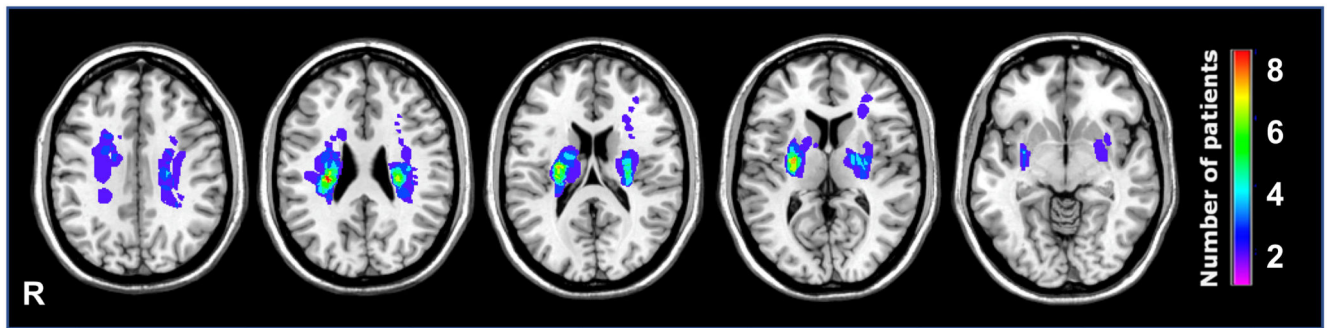


Figure 1. Stroke lesion map

Infarct lesions from 22 stroke survivors overlaid on a standardized template (MRIcron®).

The colour spectrum represented the number of stroke survivors with overlapping stroke location. All locations were subcortical regions in the middle cerebral artery territory, mostly at the corona radiata and basal ganglia. R= right side.

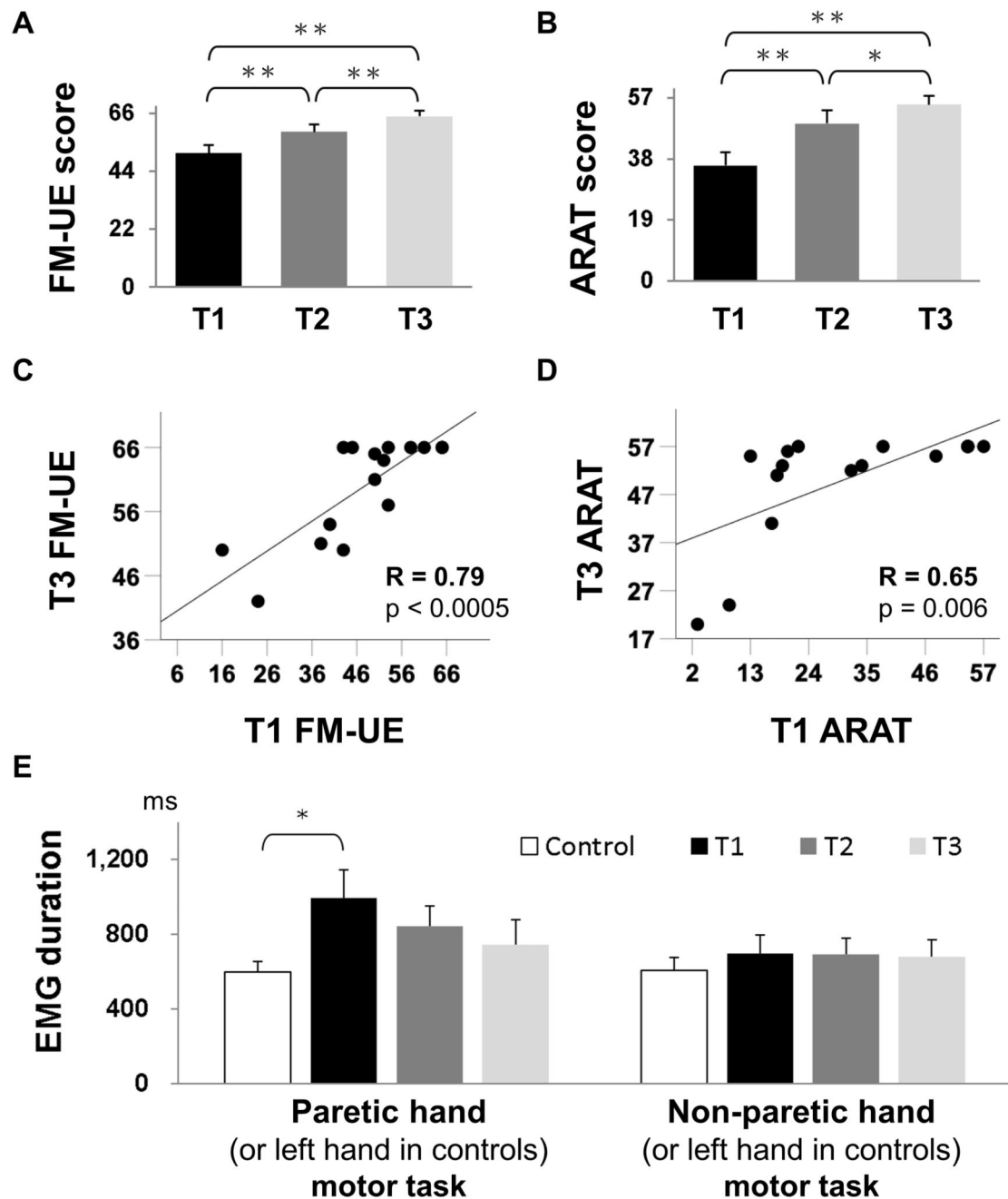


Figure 2. Motor scores and task performance measurements

(A) Fugl-Meyer upper extremity (FM-UE) test score and (B) Action Research Arm Test (ARAT) score showed significantly progressive improvements between the 3rd (T1) and 5th (T2), and between the T2 and 12th (T3) weeks after stroke onset. (C) FM-UE and (D) ARAT score at the T1 positively correlated with the corresponding motor score at T3. (E) Quantification of surface electromyography (EMG) signals during unilateral finger lifting. The EMG duration was prolonged at stroke T1 compared to the control ($p=0.017$) in paretic

hand movement, but there was no significant difference among the 3 stages after stroke or in non-paretic hand motor task. * $p<0.05$. ** $p<0.01$.



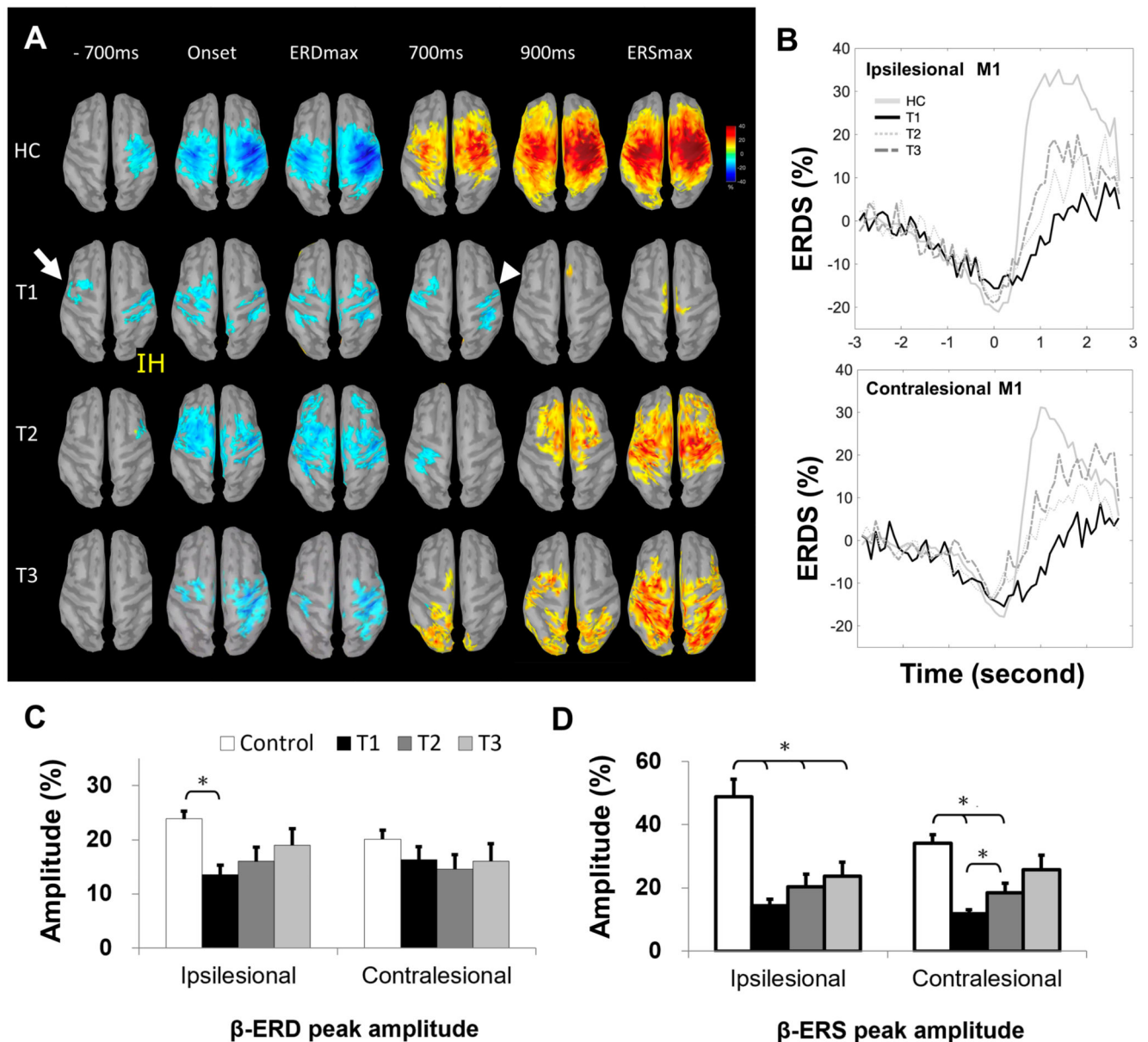


Figure 3. Motor task-dependent β -oscillations during stroke recovery (paretic hand)
(A) Topographic features of P-rhythm, event related desynchronization (β -ERD, blue), and event related synchronization (β -ERS, yellow-red) in sequential movement phases from healthy controls (nondominant left finger lifting, n=25) and right hemispheric stroke survivors (paretic left finger lifting, n=12 at T1, n=8 at T2, n=9 at T3). Topography threshold was set at $\pm 10\%$ to display all key phases among all groups. The arrow indicated early contralateral premotor cortex activation; arrowhead represented delayed ERS appearance. See Results for details. **(B)** Illustration of the group-level maximal ERD and ERS changes (power %) in the bilateral M1 from healthy controls (n=25) and all stroke survivors (n=22 at T1, n=15 at T2, n=16 at T3). **(C)** The ERD and **(D)** ERS peak amplitudes of healthy controls and stroke survivors at T1, T2, T3 in ipsilesional [right in healthy controls] and

contralesional [left in healthy controls] M1. HC= healthy control; T1, T2, T3= time of follow-ups at the 3rd, 5th, 12th weeks after stroke; IH= ipsilesional hemisphere. * $p < 0.05$



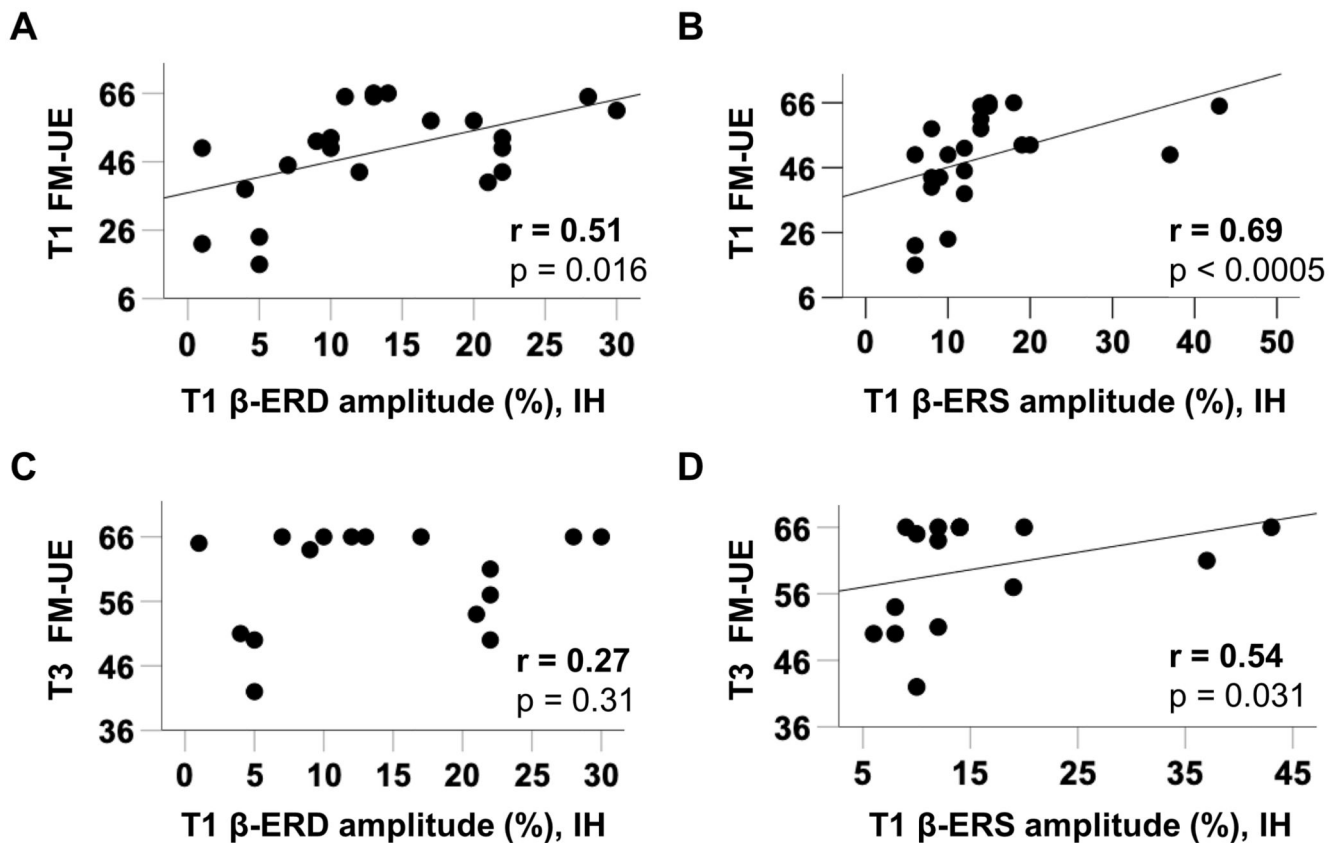


Figure 4. Functionally correlated β -oscillations in subacute stroke

(A) In subacute stroke (T1), ipsilesional primary motor cortex (M1) P-event related desynchronization (β -ERD) amplitudes positively correlated with concurrent Fugl-Meyer upper extremity (FM-UE) score. Similar correlations were also seen in action research arm test (ARAT, not shown) (B) In stroke T1, ipsilesional M1 P-event related synchronization (β -ERS) peak amplitudes positively correlated with concurrent Fugl-Meyer upper extremity (FM-UE) score. Similar correlations were also seen in ARAT (not shown) (C) Ipsilesional M1 β -ERD peak amplitudes at T1 showed no significant correlation with FM-UE at T3, partly related to ceiling effect. (D) Ipsilesional M1 β -ERS peak amplitudes at T1 positively correlated with FM-UE score at T3. T1, T2, T3= time of follow-up at the 3rd, 5th, and 12th weeks after stroke; IH= ipsilesional hemisphere.

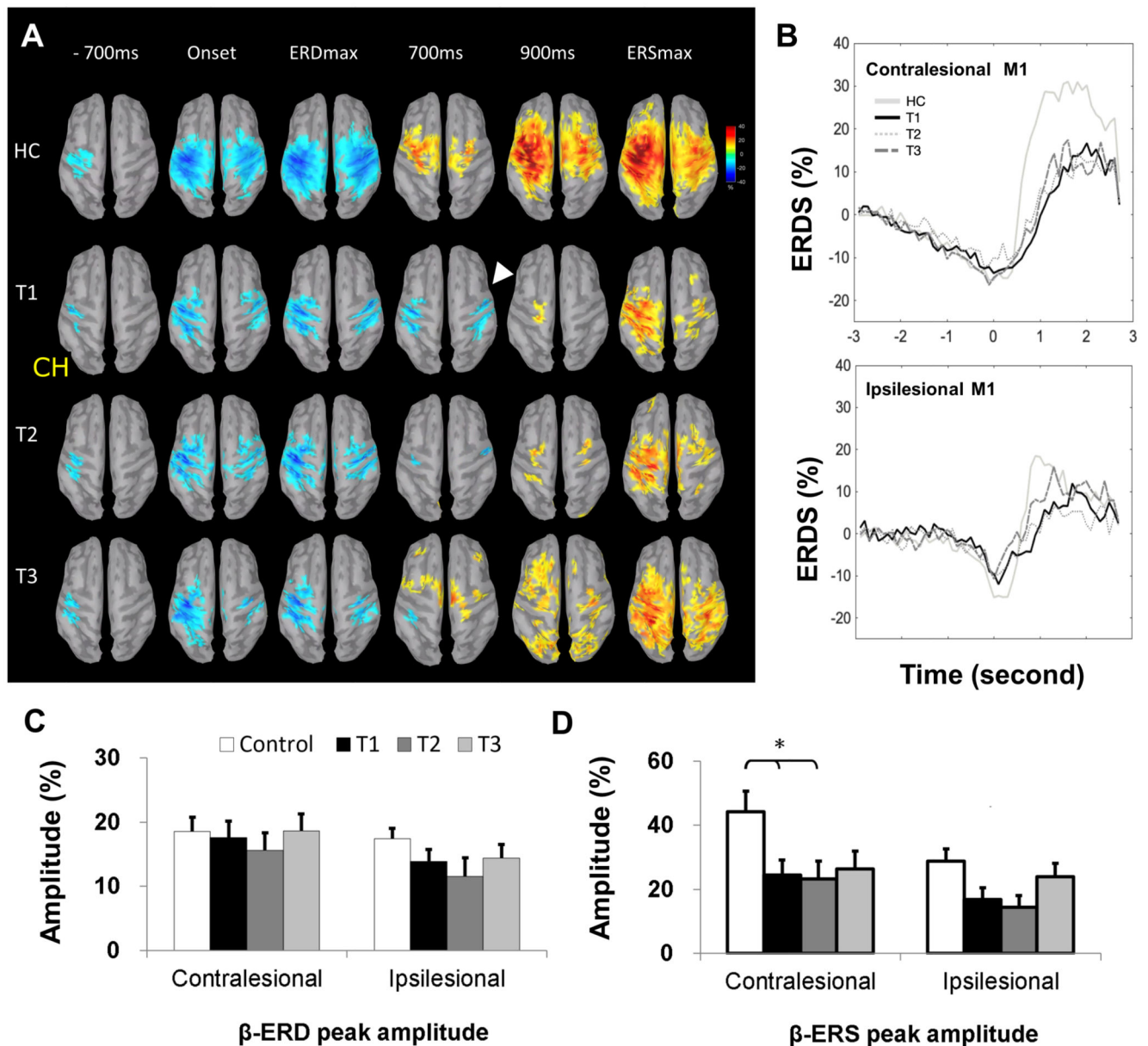


Figure 5. Motor task-dependent β -oscillations during stroke recovery (non-paretic hand)

The equivalent analyses of figure 3 in non-paretic (right in healthy controls) hand movement. **(A)** Topographic features of P-rhythm, from healthy controls (n=25) and right hemispheric stroke participants (n=11 at T1, n=7 at T2, n=9 at T3). **(B)** Illustration of the group-level maximal ERD and ERS changes (power %) in the bilateral M1 from healthy controls (n=25) and all stroke participants (n=19 at T1, n=13 at T2, n=16 at T3). **(C)** The ERD and **(D)** ERS peak amplitudes of healthy controls and stroke survivors at T1, T2, T3. HC= healthy control; T1, T2, T3= time of follow-ups at the 3rd, 5th, 12th weeks after stroke; CH= contralesional hemisphere. * $p < 0.05$ *

Table 1
Stroke Survivors Characteristics

Patient	Age	Sex	Affected hand	Post-stroke (days)	Acute	T1				T3-T1
					NIHSS	NIHSS	mRS	ARAT	FM-UE	FM-UE
1	53	M	L	19	8	4	3	18	50	11
2 [#]	71	M	L	18	4	3	3	52	58	-
3	68	F	L	16	6	5	3	9	24	18
4	55	M	R	16	14	4	3	22	43	23
5	50	M	R	24	8	5	3	17	38	13
6 [*]	57	M	L	17	3	3	2	38	50	-
7 [*]	59	M	R	14	5	2	2	57	66	-
8 [#]	61	M	R	25	4	1	1	57	66	-
9	68	F	L	20	5	1	1	54	58	8
10	55	F	L	24	4	6	3	13	50	15
11	52	M	L	14	7	3	3	34	52	12
12 [*]	43	M	L	28	5	3	1	7	22	-
13	56	M	R	16	2	1	2	54	65	1
14	61	M	R	28	6	4	3	3	16	34
15 [#]	34	M	R	21	4	4	1	57	65	-
16 [Ⓢ]	63	M	R	28	9	2	3	32	53	4
17 [Ⓢ]	62	F	L	26	8	5	3	57	61	5
18 [Ⓢ]	61	M	L	18	4	3	3	48	43	7
19 [Ⓢ]	61	M	R	28	12	4	4	20	40	14
20	60	M	L	22	6	2	3	54	65	1
21	62	F	L	26	2	1	1	19	45	21
22	59	M	R	15	8	6	3	38	53	13
Patient (n=22)	60 (55-62)	17 M/5 F	12 L/10 R	21 (16-26)	6 (4-8)	3 (2-4)	3 (2-3)	36 (18-54)	51 (43-60)	13 (7-17)
Control (n=25)	59 (42-61)	19 M/6 F	-	-	-	-	-	-	-	-

* Subjects with only time 1 evaluation

Subjects with only time 1 and time 2 evaluations

Ⓢ Subjects with only time 1 and time 3 evaluations. M = male; F = female; R = right; L = left; NIHSS = National Institutes of Health Stroke Scale; mRS = modified Rankin Scale; ARAT = action research arm test; FM-UE = Fugl-Meyer upper extremity score. T1, T3: time of follow-ups at the 3rd and 12th weeks after stroke. Data are presented as the median with interquartile range.