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Changes in mu and beta amplitude of the EEG during upper limb movement correlate with motor impairment and structural damage in subacute stroke ☆

Gadi Bartur [a,b,*], Hillel Pratt [c], Nachum Soroker [d,e]

[a] Department of Physical Therapy, Faculty of Social Welfare and Health Studies, University of Haifa, Israel
[b] Department of Physical Therapy, Reuth Medical Center, Tel Aviv, Israel
[c] Evoked Potentials Laboratory, Technion – Israel Institute of Technology, Haifa, Israel
[d] Department of Neurological Rehabilitation, Loewenstein Hospital, Raanana, Israel
[e] Sackler Faculty of Medicine, Tel Aviv University, Israel

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HIGHLIGHTS

- ERD recorded over the lesioned hemisphere correlates with EMG in the paretic arm.
- ERD magnitude also correlates with residual motor function in the paretic arm.
- ERD magnitude maintains a negative correlation with the total hemispheric volume loss.

ABSTRACT

Objective: Mu and beta EEG oscillations show typical desynchronization patterns during movement. The aim of the current study was to assess whether in sub-acute stroke patients the magnitude of movement-related desynchronization reflects the extent of residual motor ability in the paretic upper limb.
Methods: EEG and EMG data were recorded from 14 first-event stroke patients during repeated wrist extension movements of the paretic upper limb. Residual motor ability was assessed by the Fugl Meyer and Box and Blocks standardized clinical tests. Normalized lesion data was analyzed using the MEDx software.
Results: The magnitude of event-related de-synchronization (ERD) of the high-mu and low-beta bands of the EEG, measured over the affected hemisphere, correlated significantly with (a) residual motor function in the paretic upper limb as measured by standard clinical tests; (b) the magnitude of EMG recorded from the paretic upper limb during wrist extension; and (c) the total hemispheric volume loss (negative correlation).
Conclusion: The magnitude of high-mu and low-beta ERD recorded from the lesioned hemisphere of subacute stroke patients correlates with residual motor ability in the paretic upper limb.
Significance: Measures derived from quantitative EEG analysis may play an important role in neurorehabilitation clinical practice.

1. Introduction

EEG-based measures are used extensively in motor-neurophysiology research, to analyze motor learning (Gerloff et al., 1998; Wilkins et al. 2017), motor control (Erbil and Ungan, 2007), motor-system plasticity (Gerloff et al., 2006; Wilkins et al., 2017), effects of brain injury (Tecchio et al., 2005; Finnigan and van Putten, 2013) and more. They are also used as a means to assist motor recovery in brain-damaged patients (Pfurtscheller et al., 2000 Millán et al., 2010; Pichiorri et al., 2015). For example, Pichiorri and colleagues combined motor-imagery training of the paretic upper limb with brain-computer interface technology, where successful imagery was marked by stronger desynchronization in the

☆ This study was conducted in the Department of Neurological Rehabilitation, Loewenstein Hospital, Raanana, Israel.

* Corresponding author at: Department of Physical Therapy, Reuth Medical Center, Tel Aviv, Israel.
E-mail address: gadi.bartur@reuth.org.il (G. Bartur).

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alpha and beta bands (Morone et al., 2015; Buch et al., 2008; Schlögl et al., 2000).

Neural correlates of motor impairment are studied with a variety of techniques. For example, the role of disrupted connectivity in white-matter tracts was demonstrated by diffusion tensor imaging (Lindenberg et al., 2010; Chen and Schlaug, 2013; Finnigan and van Putten, 2013), and numerous studies have documented the changes in the amplitude of specific cortical EEG rhythms accompanying voluntary movement (Boyd et al., 2007). Recently, the use of biomarkers in recovery and rehabilitation research has been advocated in a consensus-based set of recommendations issued by a group of leading stroke scientists (Boyd et al., 2017). This group recommended the use of evidence based biomarkers to enhance theoretical and practical stroke research, and encouraged the development of biomarkers such as EEG, that have potential but require further substantiation in-order to serve as viable biomarkers (Boyd et al., 2017; Triccas et al., 2019). Several studies have recently tackled this challenge of examining the possible use of markers derived from EEG in the assessment of residual motor ability following brain damage (Kaiser et al., 2012; Solis-Escalante et al., 2013; Shiner et al., 2015; Chen et al., 2017; Thibaut et al., 2017; Pichiorri et al., 2018). Various protocols examining movement or movement imagery (Kaiser et al., 2012; Solis-Escalante et al., 2013; Shiner et al., 2015; Pichiorri et al., 2018) used diverse methodologies such as resting state connectivity measures (Kaiser et al., 2012; Kawano et al., 2017), oscillation power (Kaiser et al., 2012; Shiner et al., 2015; Thibaut et al., 2017), with or without assessment of motor thresholds (TMS).

In this study we tested the possible use of oscillation magnitude in the high-mu (10–12 Hz) and low-beta (12–20 Hz) frequency bands - shown in past research to be movement sensitive (Salmelin et al., 1995; Stancák and Pfurtscheller 1995; Pfurtscheller and Lopes, 1999; Frenkel-Toledo et al., 2013) - as EEG-derived bio-markers.

Specifically, we asked whether quantitative measurement of movement-related desynchronization of these EEG bands, in central electrodes C3 and C4, correlates with residual motor ability of the paretic upper limb, as reflected in standardized clinical tests, and in the EMG recorded from the moving upper-limb muscles. We also asked whether the magnitude of ERD is negatively correlated with the extent of brain tissue destruction by stroke.

2. Materials and methods

2.1. Participants

All the patients who were admitted to the Department of Neurological Rehabilitation at the Loewenstein Rehabilitation Hospital (LRH), Raanana, Israel, shortly after a first-ever event of stroke, which conformed with the strict inclusion criteria detailed below and were willing to participate were recruited, and all those who completed the tests are reported here. 14 subjects, 6 females and 8 males, aged 58 ± 15.8 years (mean ± SD) participated in the study. These patients have been recruited during a time period of about two years (2007–2009)

Inclusion criteria were: first-ever ischemic or hemorrhagic stroke; negative past history of neurological/psychiatric disease; single hemispheric stroke demonstrated in acute-stage CT scan of the brain; stable clinical and metabolic state at the time of testing; provision of informed consent. Eight patients had left- and six patients had right-hemisphere damage (LHD, RHD), all but one LHD and one RHD patient were right handed (thus, in eight patients hemiparesis affected the dominant hand and in six– the non-dominant hand). Grand average EEG time courses of a control group comprised of healthy subjects (n = 13, all right handed performing the same task as detailed below) obtained in a previous study (Bartur et al., 2015), were used as a reference for comparison with patients' EEG records. Subject recruitment and experimental protocol were approved by the LRH institutional review board. Clinical and demographic data of participants are summarized in Table 1.

2.2. Experimental procedure

Unilateral wrist-extension movement was performed repeatedly, 30 times in the non-paretic hand followed by 30 times in the paretic hand. The patients were asked to extend their wrist and fingers for 3 seconds to a rising pitch auditory cue and to relax for 3 seconds to a descending pitch cue (Fig. 1). Participants were instructed as follows: "lift your hand and fingers when you hear the ascending sound and relax them when you hear the descending sound". Subjects were comfortably seated in front of a table with the shoulders flexed and abducted to 20 degrees, and the elbows flexed to 80 degrees with forearm support on a triangular stand, so that the hand and fingers remained unsupported. The same setup was used in (Bartur et al., 2015).

2.3. EEG data acquisition and analysis

EEG was recorded with a 64 Ag-AgCl electrode cap, using the BioSemi Active Two system (BioSemiTM; http://www.biosemi.com/headcap.htm., Amsterdam, Netherlands), according to the extended 10–20 method of electrode placement. Recordings were referenced to an electrode placed on the nose and re-referenced offline to the average of all electrodes (average common reference). Surface electromyographic activity (band pass filtered between 20–256 Hz (24 dB) were collected from bilateral wrist extensors, wrist flexors and biceps muscles, only the wrist extensors were used for analysis. EOG was registered from the lateral aspect of the right eye to detect eye movement artifacts. EEG and EMG channels were sampled at 1024 Hz and low pass filtered at 256 Hz. Data was analyzed offline using Brain Vision Analyzer software (Brain Products; www.brainproducts.com; Gilching, Germany). Raw EEG recordings were band-pass-filtered offline between 1–40 Hz (24 dB). Eye movement artifacts were corrected using an Independent Component Analysis (ICA) procedure (Makeig et al., 1996; Jung et al., 2000; Delorme and Makeig, 2004). A detailed description of the preprocessing procedures has been described in detail in a previous study (Bartur et al., 2015).

Table 1
Patients' demographic and clinical data.

Patient	Age/ Gender	Lesion Side/type	Volume loss cc	TAO (days)	FM	B&B	EMG%
707	63/F	L/I	6.80	18	49	30	59.52
710*	61/F	L/I	25.71	25	13	0	0.85
717	65/F	L/I	7.61	40	–	–	43.67
906	68/M	L/I	12.68	36	14	0	4.70
907	60/M	L/I	1.16	13	61	49	55.61
909	79/M	L/I	1.15	21	16	0	17.11
910	76/M	L/I	2.88	35	30	10	222.54
911	61/M	L/I	0.81	19	53	28	45.43
706	38/F	R/I	1.77	66	43	6	6.05
709*	69/M	R/I	33.19	14	47	11	64.55
718	41/F	R/I > H	80.67	103	38	9	11.41
719	32/F	R/I	20.53	71	19	0	2.58
720	68/M	R/I	47.69	71	37	9	35.97
908	31/M	R/H	8.96	99	21	0	3.59

* Patients 710 and 709 were left handers, all others right handers; I = infarct, H = hemorrhage, L = left, R = right, TAO = time after onset (days); FM = Fugl Meyer, B&B = Box and Blocks, EMG % = EMG magnitude in the paretic upper limb relative to non-paretic limb (see text).

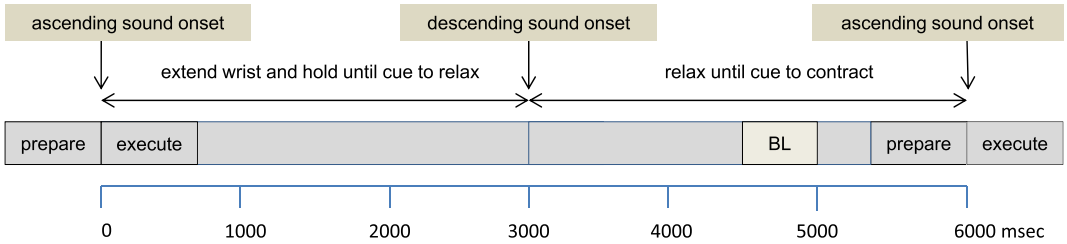

Fig. 1. Wrist extension movement cycle. The time course of a single six second experimental cycle in the wrist extension task.

Standard Event Related Desynchronization (ERD)/Event Related Synchronization (ERS) computation was conducted based on the method described by Pfurtscheller and Lopes da Silva (1999). ERD/ERS power was defined as the percentage of power difference in each movement stage in relation to the baseline period and was used as the dependent variable, with negative values indicating suppression or ERD and positive values indicating enhancement or ERS. We used a 6-second movement cycle as in our former study (Bartur et al., 2015) in which we were able to show in healthy subjects 'Movement Preparation' and 'Movement Execution' stages differing in their electrophysiological activity patterns, within this time period. The relatively short cycle (6 s) was found to be suitable for use with neurological patients with variant severity of arm paresis and motor fatigue (Bartur et al., 2018). The cycle consists of a 3-second wrist extension activity (lift plus hold) and a 3-second rest period which includes the 'Movement Preparation' stage immediately before the next cycle commences. The ERD calculation is based on comparison to a 500 ms 'Baseline' epoch within the rest period [1500 till 1000 ms before EMG onset]. Preparation stage was defined as an epoch of 700 ms immediately prior to EMG onset, and the Execution stage was defined as a period of 700 ms starting with EMG onset (Fig. 1). The 'Baseline' epoch is thus as far as possible before movement onset (to avoid overlap with the 'movement preparation' stage) and also as far as possible after the cessation of movement.

2.4. Measures

We investigated the EEG activity at central electrode locations from both hemispheres (electrodes C3 & C4), as in Bartur et al., 2015, in the course of repetitive unilateral wrist-extension movements. The analysis was conducted in two discrete frequency bands, known to exhibit distinct changes during preparation and execution of movement: low beta (12–20 Hz) and high (10–12 Hz) alpha (mu). The beta range has been shown to exhibit high EEG-EMG coherence in movement (Baker, 2007; Chakarov et al., 2009) and in observation of movement (Puzzo et al., 2011). The high mu rather than the conventional 8–12 Hz wide mu band was assessed since the high mu had been found to be more specifically associated with movement (Frenkel-Toledo et al., 2013; Vukelić et al., 2014).

EMG activity was recorded from the wrist-extensor muscles on both sides. Pairs of surface Ag-AgCl electrodes were placed 3 cm apart, oriented parallel to the long axis of the wrist extensor muscles group, the proximal electrode was placed two fingerbreadths distal to the lateral epicondyle over the mid-dorsal aspect of the forearm, and the distal electrode 3 cm distally (Dimitrijević et al., 1996). Rectified EMG onset times were used as the reference point for EEG analysis (Shibasaki and Hallett 2006). EMG magnitude of the paretic upper limb (PUL) was expressed as a percentage relative to the magnitude of the homologue muscle of the non-paretic upper limb (NUL) ($EMG_{PUL}/EMG_{NUL} * 100$). EMG amplitude is an objective physiological measure (Basmajian and De Luca 1985) of muscle activity shown to exhibit high coherence with cortical beta range during movement (Chakarov et al., 2009).

The standardized Box and Blocks (B&B) test (Mathiowetz et al., 1985) served as a behavioral measure of UL motor dexterity and the Fugl Meyer (FM) assessment (Fugl-Meyer et al., 1975), a highly valid and reliable measure of impairment shown to be a good predictor of upper limb recovery (Gladstone et al., 2002), was used to quantify motor impairments in the PUL.

2.5. Lesion analysis

The extent of brain damage of patients was calculated by analyzing follow-up CT scans dating on average 45 days post-stroke onset. The Analysis of Brain Lesions (ABLe) module implemented in MEDx software (Medical Numerics, Sterling, VA, USA) was used to analyze lesion size and location. Lesion borders were manually drawn on the digitized CTs using the MEDx software. Registration accurateness of the scans to the MNI template (explained in Solomon et al., 2007) was greater than 90% for all but two LHD patients (with 88.31% and 86.94% registration accuracy). ABLe characterizes brain lesions in MRI and CT scans of the adult human brain by spatially normalizing the lesioned brain into Talairach space using the Montreal Neurological Institute (MNI) template brain. It reports anatomical structures in the normalized brain by using an interface to the Talairach Daemon (San Antonio, Texas), the Automated Anatomical Labeling (AAL) atlas and the White Matter Atlas (Lancaster et al., 2000; Tzourio-Mazoyer et al., 2002; Solomon et al., 2007). Finally, a quantification of the volume of tissue injury contained by each structure/region of the brain was acquired (as described by us earlier in Haramati et al., 2008).

The extent of brain damage was correlated with the magnitude of ERD and with the measures of upper limb motor function (EMG, B&B and FM). Voxel-based lesion-symptom mapping (VLSM) (Bates et al., 2003), implemented in MEDx/ABLe, served to assess regions of the brain where damage significantly affected the ERD patterns and the above functional measures. VLSM quantifies lesion impact on behavior in a voxel-by-voxel manner. For each voxel of the normalized brain, a t-test is computed to assess whether patients in whom the voxel is damaged are significantly impaired relatively to patients in whom the voxel is intact. The minimal group size for analysis was set to 3 patients affected in a voxel. Only clusters of more than 10 contiguous voxels in which the t-test remained significant after False Discovery Rate (FDR) correction for multiple comparisons are presented (Benjamini and Hochberg, 1995), and brain structures of the AAL and White-Matter atlases in which 5% or more of the structure's volume is occupied by clusters of 'significantly affected' voxels are reported.

2.6. Statistical analysis:

Spearman's correlations were computed across subjects, between the percentage of ERD in the high-mu and low-beta EEG bands during wrist-extension movement (as recorded from C3 and C4 electrodes), and: (a) EMG %; (b) FM score (available from

13 patients); (c) B&B score (available from 13 patients); and (d) the percentage of volume loss in AAL determined brain structures (AAL labels) and the percentage of total brain volume loss obtained from MEDx/ABLe. The Spearman's non-parametric rank correlation measure was used owing to the relatively small number of patients (n = 13 or 14) and since it is less sensitive to outliers (Fig. 2). Voxel-based lesion-symptom mapping was performed as described above.

3. Results

3.1. Brain physiology and behavioral measures

Spearman's correlation analysis between the percentage of high-mu and low beta event-related desynchronization (ERD %), during active wrist-extension in the movement cycle (Fig. 1), and measures of motor function in the paretic upper limb revealed a significant (FDR corrected) correlation in the high mu range, while the low beta range showed a similar trend (higher motor ability correlated with more negative ERD % values, i.e., greater ERD magnitude). This was found only for ERD % values from the affected but not the unaffected hemisphere (see Table 2).

As can be seen in Table 2, the magnitude of high-mu and low beta desynchronization in the lesioned hemisphere during wrist extension movement in the paretic upper limb, correlated significantly with the FM score, the B&B score, and the EMG% value. As can be noted (bottom part of Table 2), the EMG% value, measuring recruitment of muscle units in the paretic upper limb relative to the non-paretic upper limb, correlated significantly with the two behavioral measures used to assess residual upper limb function – the FM score and the B&B score. The correlation between ERD magnitude and the measures of residual upper limb function - FM and B&B test scores and EMG% - is shown in Fig. 2.

The time-course of ERD/ERS in the low beta and high mu frequency ranges for sub groups of patients with severe and mild hemiparesis is shown in Fig. 3, compared to the grand average of healthy controls (from a previous study (Bartur et al., 2015).

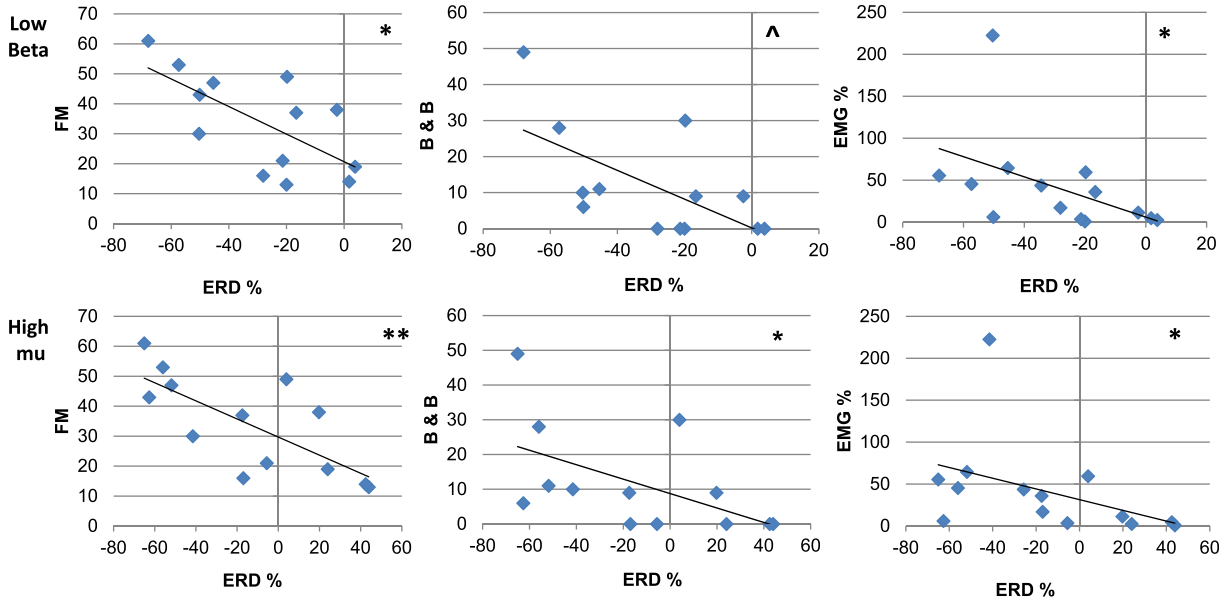

Fig. 2. Correlation between behavioral measures of upper limb paresis and ERD magnitude. Spearman correlations between %ERD in the low-beta and high-mu ranges and behavioral measures (Fugl Meyer (FM), Box and Blocks (B&B) and EMG%, see text for explanation) of residual function of the hemiparetic upper limb. **p < 0.001, *p < 0.05, ^borderline p = 0.051.

Table 2
Spearman's correlation analysis.

Variable 1	Variable 2	Hemisphere	Spearman's Rho	P value	P_{FDR}
high mu ERD	FM	non-lesioned	−0.220	0.943	0.943
	B&B		−0.100	0.740	0.792
	EMG%		−0.250	0.380	0.570
	FM	lesioned	−0.753	**0.003**	**0.027**
	B&B		−0.640	**0.019**	**0.057**
	EMG%		−0.640	**0.014**	**0.050**
low beta ERD	FM	non-lesioned	−0.090	0.748	0.792
	B&B		−0.136	0.658	0.790
	EMG%		−0.147	0.645	0.790
	FM	lesioned	−0.560	**0.046**	0.092
	B&B		−0.552	**0.051**	0.092
	EMG%		−0.587	**0.027**	0.069
EMG%	FM		0.670	**0.012**	**0.050**
	B&B		0.832	**0.000**	**0.000**

ERD = desynchronization during wrist extension movement of the paretic upper limb. More negative values denote larger ERD magnitude, thus, negative Spearman's Rho values denote a positive correlation with the ERD magnitude; Hemisphere – non-lesioned / lesioned denotes electrode side for ERD measurement; FM = Fugl Meyer score; B&B = Box and Blocks test score; EMG% = EMG magnitude in the paretic upper limb relative to the non-paretic upper limb (see text).

3.2. Lesion impact on brain physiology and behavior

Total hemispheric volume loss in the 6 RHD patients included in this analysis ranged from 1.7 to 80.6 cc (mean ± SD: 32.14 ± 28.9 cc). In the 8 LHD patients, lesion volume ranged from 0.81 to 25.7 cc (7.3 ± 8.4 cc). Hemispheric volume loss was found to negatively correlate with the magnitude of ERD recorded from the affected hemisphere during wrist extension movement in the paretic upper limb (greater lesions associated with less negative ERD%, i.e., smaller ERD magnitude) – high mu: $R = 0.55$, $p = 0.041$; low beta: $R = 0.68$, $p = 0.007$. Lesion volume did not correlate with ERD magnitude as recorded from the non-affected hemisphere. The impact of total hemispheric volume loss on the magnitude of ERD is shown in Fig. 4A.

Given the need to correct for multiple comparisons when analyzing lesion impact on behavior by VLSM, false negative results are common with this method, especially with small patient groups exhibiting marked inter-personal variance (see lesion overlap maps in Fig. 4B, C). Indeed, no region/structure in the RHD group (n = 6) contained voxel clusters that survived the FDR correction for multiple comparisons when analyzing the effect of damage on ERD magnitude, EMG, B&B and the FM test. In the LHD group (n = 8), VLSM revealed a few anatomical structures in which the functional impact of damage did survive the FDR correction. These were the putamen, the thalamus and two components of the internal capsule - the posterior limb and the retro-lenticular region. It is of interest that damage to these four brain structures significantly affected both an EEG measure - the magnitude of low-beta ERD in the lesioned hemisphere during movement of the ipsilesional (non-paretic) upper limb, and an EMG measure of muscle recruitment in the paretic upper limb - the EMG% computed as $EMG_{PUL}/EMG_{NUL} * 100$ (see *Measures* in the Section 2). The emergence of a significant impact of damage to these four structures on the EEG and EMG, may be related to the fact that in the LHD group only subcortical structures were affected in 3 or more subjects (set as a minimum for VLSM analysis, as explained in the methods section). In the LHD group, VLSM did not reveal a significant effect of damage on both the B&B and the FM test.

4. Discussion

The findings of this study show that brain physiology indices derived from EEG analyses correlate with residual motor capacity in stroke survivors. Specifically – the magnitude of desynchronization (ERD) shown in the high-mu and low-beta frequency bands of the EEG, as recorded over the lesioned hemisphere during repetitive wrist-extension movements of the paretic upper limb – was found to correlate with the magnitude of the EMG signal registered from the wrist extensor muscles in this condition. The magnitude of desynchronization (ERD) shown in the high-mu and low-beta frequency bands of the EEG correlated also with the residual motor capacity of the paretic upper limb, as reflected in test scores of widely used standardized clinical tests (Fugl Meyer; Box and Blocks).

In addition, the magnitude of ERD computed from the EEG recorded over the lesioned hemisphere, was affected in a proportional manner by the extent of hemispheric volume loss. In the LHD group, a direct relationship between ERD magnitude and lesion extent could also be shown for discrete brain structures within the thalamo-capsular-putaminal region. It is of interest that the same structures within this area that were found to exert a significant effect on ERD magnitude during wrist-extension movements of the paretic upper limb, also significantly affected the EMG registered from the acting wrist-extensor muscles. The impact of tract lesions on residual motor capacity, especially lesions affecting the cortico-spinal tract in its passage within the posterior limb of the internal capsule, is well known, and corresponds with DTI-based analyses of structure-function relationships (Lindenberg et al., 2010; Qiu et al., 2011). Thus, the findings of the present study demonstrate the connection between lesion characteristics and specific measures of physiological brain activity after stroke.

An earlier study by Page and colleagues (Page et al., 2013) on a large cohort of chronic stroke patients, found no correlation between the residual motor ability of the hemiparetic upper limb and the overall extent of tissue damage (Page and colleagues did not aim to correlate motor ability with the extent of damage to specific regions of interest). We also failed to reveal a direct rela-

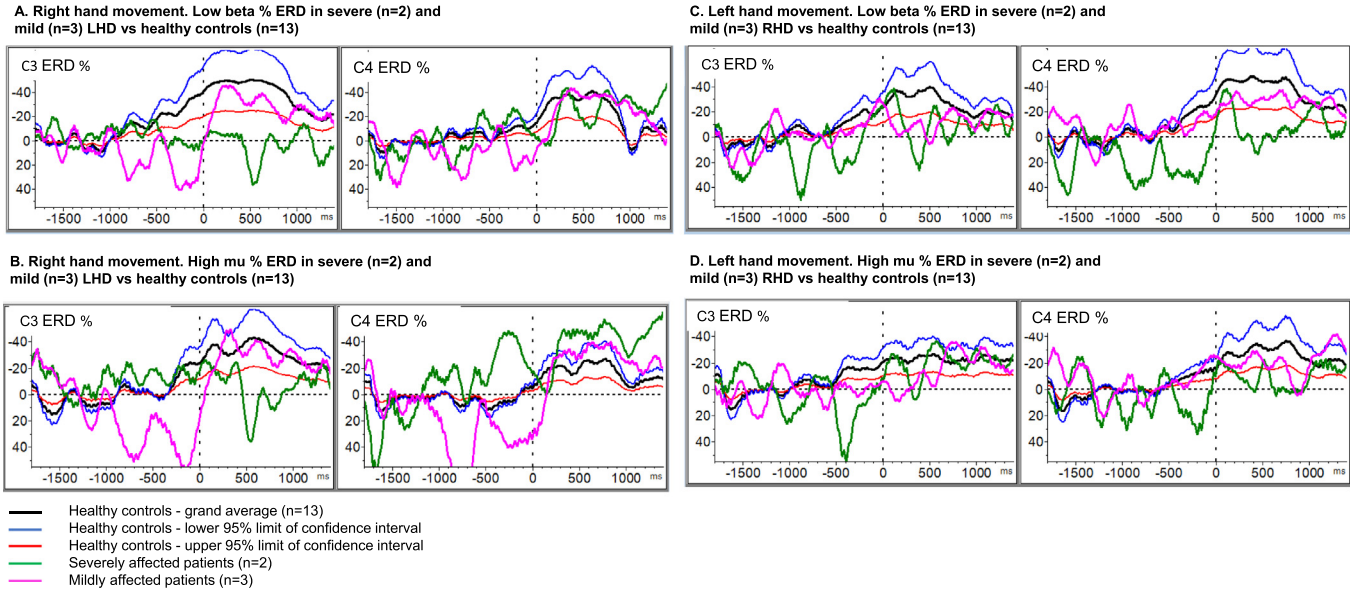

Fig. 3. Low beta and high mu %ERD among LHD, RHD and healthy control subjects. %ERD (upward deflection) and %ERS (downward deflection) throughout the movement cycle, in low beta (12–20 Hz) and high mu (10–12 Hz) frequency ranges, in electrodes C3 and C4 (black line) with lower and upper 95% confidence intervals (blue and red lines respectively). Data averaged from 2 LHD patients with severe hemiparesis-green line (FM = 13, B&B = 0; FM = 14, B&B = 0), 3 LHD patients with mild hemiparesis-pink line (FM = 49, B&B = 30; FM = 61, B&B = 49; FM = 53, B&B = 28), 2 RHD patients with severe hemiparesis (FM = 19, B&B = 0; FM = 21, B&B = 0), 3 RHD patients with mild hemiparesis (FM = 47, B&B = 11; FM = 43, B&B = 6; FM = 38, B&B = 9) and 13 healthy controls. Vertical dotted line at "0" point denotes EMG onset recorded from wrist extensors at the start of movement execution, the x axis = time in milliseconds from minus 1800 until 1400 relative to EMG onset (see Fig. 1 and Methods section).

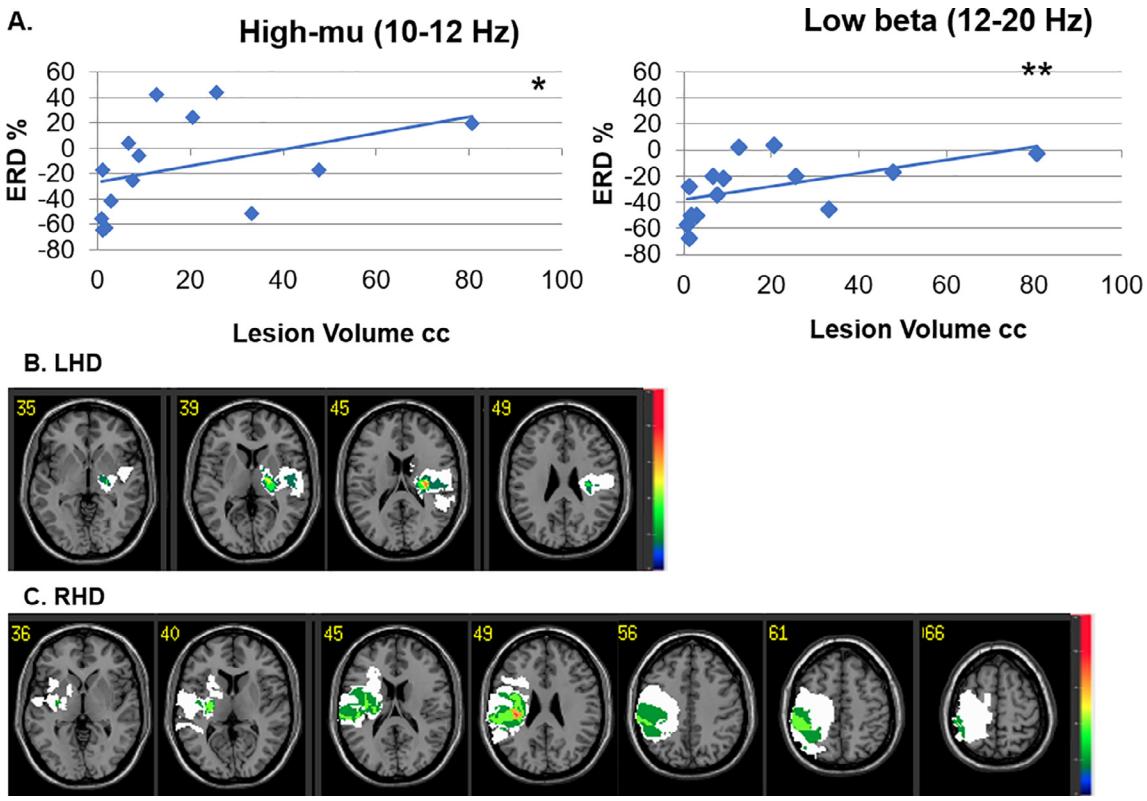

Fig. 4. %ERD correlation with lesion extent and Lesion overlap maps. Representative normalized slices showing lesion overlap in (A) left- and (B) right-hemisphere damaged patients (out of 90 normalized slices), displayed in radiological convention (right hemisphere on left side and vice versa), with warmer colors indicating greater lesion overlap: white = 1, dark green = 2, light green = 3, yellow = 4, orange = 5, orange-red = 6, red = 7, dark red = 8. (C) The effect of total hemispheric volume loss on ERD magnitude in the affected hemisphere during movement of the paretic upper limb. $^{**}p < 0.001$, $^{*}p < 0.05$.

tionship between motor ability and overall lesion size. However, in our study, the overall extent of damage, and more specifically, the amount of injury to capsual-putaminal structures, did correlate with the magnitude of movement-related attenuation of the MU and beta bands in the affected hemisphere, which in turn correlated with residual functional ability of the hemiparetic upper limb and with the EMG amplitude in the wrist-extensor muscles of that limb. It should be noted that Page et al (Page et al., 2013) looked only at moderately affected patients in the chronic stage (i.e., at a stage where lesion impact is already largely modulated by the effects of natural and treatment-induced plasticity), while our study investigated patients with severe to moderate hemiparesis in the sub-acute stage of the disease. It remains to be shown whether spontaneous or treatment-related improvement in hemiparesis is also associated with corresponding increments in ERD magnitude.

The connection of EEG oscillations and residual motor capacity in the paretic upper limb was shown here by way of significant correlation coefficients between EEG and upper limb movement variables. Given this correlation, longitudinal assessments of ERD magnitude during movement of the paretic upper limb (especially ERD in the high-mu band) might prove to possess a predictive value, i.e., be used as a bio-marker to indicate effects of therapeutic interventions and the course of natural and treatment-induced recovery in stroke survivors. It is not at all trivial that markers derived from brain activity were found to be well correlated to the FM and B&B scores. The clinical value of having EEG-derived biomarkers relies on a. EEG being easily applicable in the clinical setting (unlike fMRI for instance); b. The ability of EEG to point not only to impairments in the motor execution stage (like EMG) but also in the preceding preparation stage of movement; and, c. The ability of EEG to point to dynamics in intra- and inter- hemispheric activity induced by interventions such as action observation or MVF. For example, it was shown recently, in stroke patients, that the magnitude of low-mu (8–10 Hz) suppression measured during action observation, maintains a significant negative correlation with the extent of damage to the right inferior parietal lobule (Frenkel-Toledo et al., 2014). Patients with damage to this region, or to the adjacent opercular region of the inferior frontal gyrus, were shown to also have an impairment in movement-imitation capacity (as measured by the standardized test of De Renzi et al., 1980). In these patients, impaired movement-imitation (a major sign of ideomotor apraxia) was found to correlate negatively with the magnitude of low-mu suppression during action observation (Frenkel-Toledo et al., 2016). Given the fact that these specific cortical regions contain the major parts of the human mirror-neuron system (Rizzolatti and Sinigaglia 2010), these findings point to a role for quantitative measurement of low-mu suppression in monitoring the recruitment of mirror neurons by different interventions. Such measurement may help assess the likely benefit of rehabilitation based on action observation to patients with different lesion characteristics. In the current study, participants could see the movement of the performing upper limb. Further study – comparing EEG dynamics in this condition with a control condition where movement is concealed from vision - is needed in order to assess in what way movement observation affected the current results.

Another physiological variable whose quantitative measure was shown to be important in monitoring the effects of interventions is the magnitude of low-beta desynchronization during upper-limb movement. In recent studies on the mechanism of improvement induced by mirror visual feedback, i.e., the execution of movement in one limb when a mid-sagittal mirror reflecting the movement makes it appear as movement in the contralateral limb, see

(Ramachandran and Altschuler, 2009), the effect of the mid-sagittal mirror was to attenuate the magnitude of low-beta ERD in the hemisphere contralateral to the actually active upper limb. This effect, in turn, reduced the hemispheric asymmetry that is normally observed during unilateral upper-limb movement (Bartur et al., 2015). It remains to be shown whether clinical success with this intervention method in stroke patients correlates with the amount of attenuation of the low-beta ERD over the non-lesioned hemisphere. Other uses of quantitative measures derived from scalp EEG recording are seen in the rapidly expanding clinical utilization of devices using brain-computer interface (BCI) to enable basic environmental control to severely disabled persons and for rehabilitation training purposes (e.g., Daly and Wolpaw, 2008; Pichiorri et al., 2015).

The association between movement execution and desynchronization of the mu and beta bands has been well documented for years (see, Pfurtscheller et al., 2000). However, the neural processes underlying movement-related desynchronization in these two bands is understood only in part (Engel and Fries 2010). The mu band desynchronization has been suggested to reflect a wide-spread activity within the motor system while beta desynchronization reflects activity that is connected to motor execution in a more discrete manner (Aono et al., 2013). Beta-band dynamics was described also in conjunction with processing of cognitive aspects related to the motor act (Engel and Fries 2010; Zaepffel et al., 2013). For instance, cue predictability was shown to affect the magnitude of alpha and beta band oscillations (Alegre et al., 2003), with predictable cues associated with earlier onset and larger magnitude of ERDs relative to random cues. Thus, the predictable auditory cues used in the current study to denote movement onset and offset probably influenced the magnitude of the ERD. Moreover, observing exaggerated beta ERS, or beta ERS where beta ERD is expected (e.g., during movement execution), has been suggested to indicate pathological inhibition. This has been shown in patients suffering from Parkinson's disease during the off period (Engel and Fries, 2010). The results of the current study are in line with this premise, where more severely affected patients showed very weak ERD magnitude or even ERS during the movement execution stage, while a clear ERD was seen in more mildly affected patients and in healthy controls (see Fig. 3).

The observed correlation between ERD magnitude and the magnitude of the EMG signal recorded from the paretic wrist-extensor muscle, could possibly reflect merely the power volitionally executed by the patient and not necessarily the severity of his/her hemiparesis. However, ERD magnitude correlated here not only with the EMG recorded from the acting muscle (which could be activated with more or less force upon the patient's will) but also with standardized tests used in clinical practice to quantify the severity of motor impairment (the Fugl Meyer and the Box and Blocks). These two clinical measures in themselves correlated with the EMG. Moreover, ERD magnitude correlated with total lesion volume, and this cross correlation supports the conjecture that the ERD as measured here represents the severity of hemiparesis rather than the force volitionally exerted by the patient.

Our results support the use of quantitative measures of desynchronization for clinical purposes. In our case - as a marker of residual capacity within the damaged motor system following unilateral hemispheric damage. Our data seem to put the high-mu band at an advantage (based on correlation strength) over the low-beta band, as a neurophysiological marker of residual motor capacity.

Declaration of Competing Interest

None of the authors have potential conflicts of interest to be disclosed.

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