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How does upper extremity Fugl-Meyer motor score relate to resting-state EEG in chronic stroke? A power spectral density analysis

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HIGHLIGHTS

- Asymmetry of EEG power in chronic stroke survivors is higher compared to controls.
- Asymmetry of EEG power is related to the Fugl-Meyer motor assessment of the upper extremity.
- Findings were most pronounced in the delta and theta frequency bands.

ABSTRACT

Objective: We investigated the potential added value of high-density resting-state EEG by addressing differences with healthy individuals and associations with Fugl-Meyer motor assessment of the upper extremity (FM-UE) scores in chronic stroke.
Methods: Twenty-one chronic stroke survivors with initial upper limb paresis and eleven matched controls were included. Group differences regarding resting-state EEG parameters (Delta Alpha ratio (DAR) and pairwise-derived Brain Symmetry Index (BSI)) and associations with FM-UE were investigated, as well as lateralization of BSI and the value of different frequency bands.
Results: Chronic stroke survivors showed higher BSI compared to controls ($p < 0.001$), most pronounced in delta and theta frequency bands ($p < 0.0001$; $p < 0.001$). In the delta and theta band, BSI was significantly negatively associated with FM-UE (*both* $p = 0.008$) corrected for confounding factors. DAR showed

Abbreviations: BSI, Brain Symmetry Index; DAR, Delta Alpha Ratio; FM-UE, Fugl-Meyer motor assessment of the upper extremity; NIHSS, National Institutes of Health Stroke Scale.

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no differences between groups nor association with FM-UE. Directional BSI showed increased power in the affected versus the unaffected hemisphere.
Conclusions: Asymmetry in spectral power between hemispheres was present in chronic stroke, most pronounced in low frequencies and related to upper extremity motor function deficit.
Significance: BSI is related to motor impairment and higher in chronic stroke patients compared to healthy controls, suggesting that BSI may be a marker of selective motor control.

1. Introduction

Stroke is one of the main causes of serious disability in adults nowadays (WHO, The World Health Report, 2003). 80% of acute stroke survivors suffer from paresis of the upper extremity (Cramer et al., 1997). The Fugl-Meyer motor assessment of the upper extremity (FM-UE) often serves as the primary outcome measure for quantifying behavioural restitution in clinical trials, in particular in the field of upper limb robotics (Veerbeek et al., 2017). FM-UE is considered reliable and valid for measuring motor function (Sanford et al., 1993; Duncan et al., 1983; Gladstone et al., 2002). It assesses the patient's ability of moving outside the abnormal synergistic dependent motor patterns and reflects patient's control of selective and isolated joint movements (Twitchell, 1951; Fugl-Meyer et al., 1975; McMorland et al., 2015). However, the FM-UE is an indirect measure of neural deficits, and its relation with direct biomarkers of cortical state is still underexplored. Knowledge about the association between severity of upper limb motor impairment and cortical activity, measured with non-invasive techniques such as EEG, can be of value to provide more insight into the cortical reorganization accompanied with stroke recovery.

Presence of low frequency oscillations in the EEG signal have been associated with cerebral dysfunction (Andraus and Alves-Leon, 2011) including neural deficits post stroke (Van Putten and Tavy, 2004; Finnigan and Van Putten, 2013). The Delta Alpha ratio (DAR) and the pairwise-derived Brain Symmetry Index (BSI) are resting-state EEG parameters which are potentially valuable early predictors of neurological function in stroke survivors (Finnigan et al., 2016). DAR is the ratio between the spectral power in the delta and alpha frequency band. For adults in awake state, increased low-frequency components like delta and theta oscillations reflect cerebral dysfunction (Britton et al., 2016), while preserved activity in the alpha frequency band represents general well-functioning (Bazanova, 2012). The pairwise-derived BSI, which is a variation on the original BSI (Van Putten and Tavy, 2004), reflects the amount of asymmetry in spectral power of the EEG signal between homologous channels forming pairs over the affected and unaffected hemisphere (Sheorajpanday et al., 2009).

Both DAR and BSI are increased in the (sub) acute phase post stroke (Sheorajpanday et al., 2009; Finnigan et al., 2016; Agius Anastasi et al., 2017). However, it is still unknown whether these power spectral density measures differ between chronic stroke survivors when compared to healthy individuals and whether they are related to motor impairment reflected by the FM-UE. Moreover, BSI analysis might be improved by considering the value of frequency bands and directionality of asymmetry.

The aim of the current study was to address the potential added value of resting-state EEG as a biomarker for neurological recovery post stroke. Therefore, we investigated whether chronic stroke survivors deviate from healthy individuals regarding their resting-state power spectral densities, in particular the resulting measures DAR and BSI. In addition, we studied the association between DAR/BSI and FM-UE scores in chronic stroke. We hypothesized that DAR and BSI of chronic stroke survivors are increased compared to healthy subjects and negatively associated with FM-UE scores. For the BSI, this was expected to be specifically the case in the lower frequency bands (delta and theta) since these are most affected in stroke (Britton et al., 2016).

2. Methods

The study was approved by the Medical Ethical Reviewing Committee of the VU University Medical Center Amsterdam (registration number 2014.140) and carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

2.1. Subjects

Twenty-one chronic stroke survivors were included in this study (15 males; mean age, 60.6; range, 48–77). Patient characteristics can be found in Table 1. The inclusion criteria were: (1) a first-ever cerebral stroke; (2) $\geq$6 months post stroke; (3) initial upper limb paresis in the acute phase; (4) $\geq$18 years of age; (5) Mini Mental State Examination score $\geq$20 and (6) written informed consent. Exclusion criteria were: (1) a pacemaker or other metallic implants; (2) upper extremity orthopaedic limitations present before stroke onset; (3) recurrent stroke. Furthermore, eleven healthy age- and gender- matched controls without a history of neurologic disorders were recruited (7 males; mean age, 58.5; range, 42–75).

2.2. Procedure

All participants provided written informed consent. Clinical tests were performed by the chronic stroke group. Resting-state EEG was measured in a specially equipped van, which allowed for visiting participants at their current residence. Five consecutive trials of one minute each were recorded. Participants were measured while seated in a wheelchair with eyes opened. Participants were asked to focus on a dot that was presented on a computer screen just below eye level to prevent drowsiness and artefacts due to eye movements. One hospital visit was required for a structural MRI measurement of the brain.

2.3. Data acquisition

2.3.1. Electroencephalography

A high-density 64-channel EEG recording was performed using an EEG cap with Ag/AgCl electrodes ordered according to the international 10–20 system and a multichannel amplifier (Refa, TMSi, Oldenzaal, the Netherlands). Electrodes located at the mastoids (m1, m2) were not used, resulting in a 62-channel recording. Recordings were performed at a rate of 2048 Hz using ASA soft-

Table 1
Patient characteristics.

ID	Age	Gender	Time PS	Affected hemisphere	Lesion location	FM UE	NIHSS	MI UE	MI LE	DAR	BSI	BSI_{delta}	BSI_{theta}	BSI_{alpha}	BSI_{beta}
1	64	M	82	R	C-SC	13	3	28	72	4.40	0.215	0.356	0.319	0.141	0.183
2	62	M	49	L	C	39	3	70	77	2.17	0.242	0.174	0.117	0.187	0.342
3	77	M	7	R	C-SC	62	0	83	91	3.62	0.150	0.184	0.192	0.217	0.115
4	66	F	212	L	C-SC	9	9	23	48	1.50	0.201	0.296	0.253	0.167	0.171
5	76	F	35	R	C	63	2	76	72	1.14	0.147	0.171	0.145	0.097	0.166
6	54	M	21	R	C-SC	8	7	39	64	13.57	0.240	0.297	0.178	0.114	0.268
7	67	M	26	L	C-SC	54	1	76	75	1.15	0.163	0.236	0.285	0.112	0.127
8	55	M	75	R	C-SC	58	0	91	100	2.52	0.174	0.313	0.229	0.128	0.132
9	59	M	70	R	C-SC	9	4	28	64	1.20	0.194	0.217	0.274	0.298	0.139
10	68	F	67	L	C	66	0	84	100	1.57	0.118	0.081	0.090	0.105	0.163
11	49	F	40	R	C	59	1	72	91	0.88	0.150	0.129	0.163	0.205	0.148
12	57	M	10	R	C	66	0	100	100	7.39	0.257	0.139	0.131	0.249	0.340
13	48	M	80	R	C-SC	10	5	23	28	2.87	0.173	0.265	0.269	0.119	0.146
14	65	M	22	R	C	64	2	100	91	0.49	0.166	0.156	0.102	0.082	0.236
15	50	F	53	L	C-SC	59	1	100	80	2.79	0.103	0.078	0.098	0.117	0.119
16	50	M	34	L	C-SC	48	1	65	53	2.94	0.137	0.173	0.130	0.160	0.116
17	56	M	10	R	C-SC	56	0	76	83	2.98	0.194	0.252	0.324	0.241	0.112
18	48	M	88	L	C	66	0	100	100	3.38	0.117	0.140	0.101	0.098	0.130
19	61	F	10	L	C-SC	60	3	76	91	3.50	0.190	0.177	0.170	0.213	0.194
20	72	M	15	R	C-SC	26	4	54	72	2.12	0.221	0.300	0.207	0.137	0.220
21	68	M	142	R	C-SC	20	5	39	72	4.51	0.225	0.397	0.377	0.136	0.143

ID: Subject number; Age (years); Gender (M: male, F: female); Time PS: Time post stroke (months); Affected hemisphere (L: left, R: right); Lesion location (C: cortical, C-SC: cortical-subcortical); FM-UE: Fugl-Meyer motor assessment score of the upper extremity [0–66]; NIHSS: National Institutes of Health Stroke Scale [0–42]; MI UE/LE: Motricity Index Upper Extremity/Lower Extremity [0–100]; DAR: Delta Alpha power Ratio; BSI: pairwise derived Brain Symmetry Index; $BSI_{delta/theta/alpha/beta}$: BSI over a specific frequency band.

ware (ANT software BV, The Netherlands). The ground electrode was placed on the mastoid process. Signals were recorded to average reference. Electrode impedances were kept below 20 kΩ.

2.3.2. Clinical tests

A sensitive, valid and reliable clinical test to measure the motor function of the upper limb at the impairment level is the upper extremity domain of the Fugl-Meyer motor assessment, (FM-UE) (Duncan et al., 1983; Sanford et al., 1993; Gladstone et al., 2002). The FM-UE is an impairment scale specific for stroke survivors and determines the ability to execute dissociated movements with the upper paretic limb (Fugl-Meyer et al., 1975). It is a valid predictor of upper extremity motor recovery and is suggested to reflect most appropriately 'true' neurological motor recovery (Krakauer, 2005), in the body structure and function domain of the International Classification of Functioning, Disability and Health (ICF) model. A higher score corresponds to better motor function, with a maximum score of 66. The National Institutes of Health Stroke Scale (NIHSS) served to quantify stroke severity. Lower NIHSS scores correspond to less neurological impairments; the maximum score of this test is 42. Motricity Index of the upper (MI-UE) and lower extremity (MI-LE) was performed in order to provide information on the level of paresis. The maximum score is 100 for each extremity separately.

2.3.3. Lesion localization

Structural magnetic resonance images of each participant were obtained at the VU Medical Center, Amsterdam. T1-weighted volumes were acquired with a Discovery MR750 3 Tesla scanner (GE, Waukesha, WI, USA) running a 3D fast spoiled gradient-recalled-echo sequence. The volume consisted of 172 sagittal slices (256×256). The scans were reviewed by a certified radiologist, where after lesions were rated as cortical, subcortical or cortical-subcortical, in line with the Automated Anatomical Labelling atlas. Furthermore, the clinically obtained information on the side of the affected hemisphere (left/right) was checked based on the MRI data, which did not show discrepancies.

2.4. Data analysis

2.4.1. Pre-processing

Offline analysis was realized using Matlab (R2012a, The Mathworks, Natwick, MA) using the FieldTrip toolbox for EEG/MEG-analysis (Oostenveld et al., 2011). EEG data were filtered with a 4th order high-pass Butterworth filter (cut-off at 0.5 Hz). Powerline artefacts were reduced using notch filters around 50, 100, and 150 Hz (4th-order bidirectional Butterworth, band-width 1 Hz). Further artefact rejection consisted of the exclusion of eye-blinks and -movements using independent component analysis (ICA) based on visual inspection of the components' waveforms and topographic distributions. Noisy channels were removed followed by re-referencing to the remaining average. Subsequently, EEG signals were divided into non-overlapping contiguous epochs of 2 s for further analyses. Spectral power was estimated after correction with a Hanning taper of window size equal to epoch length.

2.4.2. Outcome variables

2.4.2.1. Delta Alpha ratio (DAR). The DAR was defined as the ratio of the delta power to the alpha power. For every channel c the power of the delta (alpha) frequency band $f = 1, \cdots, 4$ Hz $(8, \cdots, 12$ Hz) was determined as the mean of the spectral power $P_c(f)$. With these mean values, the delta-alpha ratio was computed as

$$\mathrm{DAR_c} = \frac{\langle P_c(f)\rangle_{f=1,\cdots,4\ \mathrm{Hz}}}{\langle P_c(f)\rangle_{f=8,\cdots,12\ \mathrm{Hz}}} \tag{1}$$

Subsequently, we averaged the ratios over all N EEG channels yielding the global DAR:

$$\mathrm{DAR} = \frac{1}{N}\sum_{c=1}^{N}\mathrm{DAR_c} \tag{2}$$

2.4.2.2. Pairwise-derived Brain Symmetry Index (BSI). The BSI was defined as the absolute pairwise normalized difference in spectral power between the homologous channels c_L and c_R for left and right, respectively. The difference was averaged over a range from 1 to 25 Hz (adapted from Sheorajpanday et al., 2009) according to

$$\mathrm{BSI}_{cp} = \left\langle \left| \frac{P_{c_R}(f) - P_{c_L}(f)}{P_{c_R}(f) + P_{c_L}(f)} \right| \right\rangle_{f=1,\cdots,25\ \mathrm{Hz}} \quad (3)$$

These values were averaged over all channel pairs *cp*:

$$\mathrm{BSI} = \frac{2}{N} \sum_{cp=1}^{N/2} \mathrm{BSI}_{cp} \quad (4)$$

BSI has an upper bound of one, reflecting maximal asymmetry for all channel pairs; the lower bound is zero, representing perfect symmetry. In (3) and (4), electrodes of the mid-line were excluded since they do not form channel pairs. Whenever one of the electrodes of a channel pair was considered a bad channel, the corresponding channel pair was excluded.

Next to the assessment over the range of 1–25 Hz, BSI was determined separately for the delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz) and beta (12–30 Hz) frequency band.

2.4.2.3. Directional Brain Symmetry Index. The BSI provides information on the asymmetry between the spectral powers obtained from the hemispheres. However, it does not take the direction of this asymmetry into account. For the latter, we omitted the modulus computation in (3). The resulting directional BSI (BSI_{dir}) indicates whether the power is higher in the left or right hemisphere.

$$\mathrm{BSI}_{\mathrm{dir}_{cp}} = \left\langle \frac{P_{c_R}(f) - P_{c_L}(f)}{P_{c_R}(f) + P_{c_L}(f)} \right\rangle_{f=1,\cdots,25\ \mathrm{Hz}} \quad (5)$$

Values were averaged over all channel pairs:

$$\mathrm{BSI}_{dir} = \frac{2}{N} \sum_{cp=1}^{N/2} \mathrm{BSI}_{\mathrm{dir}_{cp}} \quad (6)$$

BSI_{dir} ranges from −1 to +1 with $\mathrm{BSI}_{dir} = 0$ representing perfect symmetry. Positive values represent higher power in the right hemisphere compared to the left hemisphere, vice versa for negative values. For left side lesions, BSI_{dir} was multiplied by −1. Therefore, for stroke survivors a positive value always corresponds to higher power in the affected hemisphere compared to the unaffected hemisphere and vice versa for negative values.

2.4.3. Statistics

It was verified whether the EEG based parameters followed a normal distribution by visual inspection of the histogram and probability distribution (q-q plot) and by the Kolmogorov-Smirnov test. Resting-state EEG parameter differences between chronic stroke survivors and healthy individuals were investigated using independent-samples *t*-tests. If assumptions of normality were not met, a log transformation was applied, after which the distribution was checked again. After Bonferroni correction, the critical α-level for significance was set to 0.008 (0.05/6). Effect-sizes were estimated via Hedges' G in view of the sample sizes.

We used linear regression analysis to investigate the association between resting-state EEG parameters and motor function. Associations were tested for possible confounding factors: age, gender, affected hemisphere, lesion location, time post stroke and other neurological deficits (i.e. the sum of the affected non-motor items of the NIHSS: visual impairment, facial palsy, ataxia, sensory, aphasia, dysarthria and extinction/inattention). If the regression coefficient changed more than 10% after adding the covariate, it was considered a confounder. Subsequently, a correction was applied for the strongest confounder.

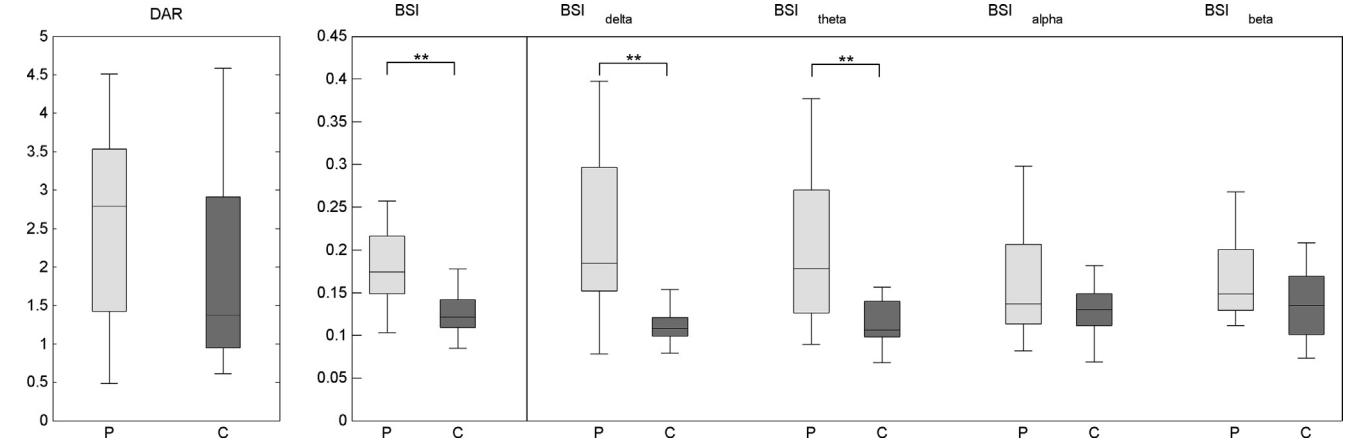
3. Results

3.1. Comparisons between chronic stroke survivors and healthy individuals

Table 1 summarizes the characteristics of the participating stroke survivors. Descriptive statistics and results of the

Table 2
Descriptive statistics and outcomes of independent-samples *t*-tests.

	Age	DAR*	BSI	BSI_{delta}	BSI_{theta}	BSI_{alpha}	BSI_{beta}
Stroke (N=21)							
Mean	60.6	2.79	0.180	0.216	0.198	0.158	0.177
SD	9.0	2.21	0.044	0.088	0.086	0.059	0.069
Controls (N=11)							
Mean	58.5	1.37	0.125	0.112	0.116	0.128	0.136
SD	9.9	2.07	0.026	0.020	0.031	0.030	0.044
t (df = 30)	0.61	1.5	4.4	5.2	3.9	1.9	1.8
p-value	0.55	0.15	<0.001	<0.001	<0.001	0.06	0.09
Effect size	0.22	0.54	1.38	1.39	1.10	0.57	0.65



N = number of participants; P = stroke patients; C = controls; SD: standard deviation; t = t-statistic; df = degrees of freedom; Effect size: reflected by Hedges' g (unbiased); DAR: Delta Alpha power Ratio; BSI: pairwise-derived Brain Symmetry Index; $\mathrm{BSI}_{delta/theta/alpha/beta}$: BSIover a specific frequency band. *Median and IQR are provided of non-transformed data instead of mean and SD, Independent samples *t*-test was performed on log-transformed data; **p < 0.001, Bonferroni corrected α-level = 0.008.

independent-samples *t*-tests can be found in Table 2. DAR was log transformed in order to attain normal distributed data before an independent *t*-test was performed. No significant differences were found between chronic stroke survivors compared to healthy individuals regarding DAR ($p = 0.15$). Chronic stroke survivors showed higher BSI values (M = 0.180, SD = 0.044) compared to healthy individuals (M = 0.125, SD = 0.026, t(30) = 4.4, $p < 0.001$, $g = 1.38$). This difference was most pronounced in the delta (Stroke: M = 0.216, SD = 0.088; Controls: M = 0.112, SD = 0.020, t(30) = 5.2, $p < 0.0001$, $g = 1.39$) and theta band (Stroke: M = 0.198, SD = 0.086; Controls: M = 0.116, SD = 0.031, t(30) = 3.9, $p < 0.001$, $g = 1.10$). No significant differences were found between the groups in BSI calculated over the alpha ($p = 0.06$) or beta frequency band ($p = 0.085$).

3.2. Association between EEG parameters and motor impairment

Associations were tested for possible confounding factors; age, gender, affected hemisphere, lesion location (based on MRI), time post stroke and other neurological deficits. In case of confounding, *other neurological deficits* emerged as most powerful, for which a correction was applied.

Raw and corrected regression coefficients of the associations between EEG parameters and FM-UE based on linear regression analyses are shown in Table 3. No significant association was found between the DAR and FM-UE ($p = 0.211$). Significant negative associations with FM-UE were confirmed for the BSI calculated over the delta and theta frequency band when corrected for other neurological deficits (delta: $b = -130$, 95%CI = −222 to −37, $p = 0.008$; theta: $b = -119$, 95%CI = −202 to −35, $p = 0.008$). No significant associations were found in the alpha or beta band ($p = 0.29$; $p = 0.67$).

Fig. 1 shows the uncorrected association between BSI_{dir} in the delta and theta frequency band and FM-UE. Increased BSI_{dir} towards the affected hemisphere in the delta and theta frequency band was associated with lower FM-UE scores corrected for other neurological deficits (delta: $b = -95$, 95%CI = −152 to −38, $p = 0.003$; theta: $b = -99$, 95%CI = −153 to −44, $p = 0.001$). Also in the alpha band a negative association between BSI_{dir} and FM-UE post stroke was found when corrected for other neurological deficits ($b = -103$, 95%CI = −188 to −19, $p = 0.020$, but not in the beta band ($p = 0.45$). Healthy individuals showed BSI_{dir} values around zero (Fig. 1).

4. Discussion

We studied the potential added value of resting-state EEG as biomarker for neurological recovery post stroke. Therefore,

Table 3
Associations between EEG parameters and Fugl-Meyer motor assessment of the upper extremity based on linear regression analyses.

Independent variable	Uncorrected				Corrected*		
	B	[95% CI]	p-value	R^2	B	[95% CI]	p-value
DAR	−2.3	[−6.0 1.4]	0.21	0.08			
BSI	−275	[−489 −61]	0.01	0.276	−145	[−350 60]	0.16
δ	−185	[−273 −97]	<0.01	0.505	−130	[−222 −37]	**<0.01**
θ	−158	[−261 −54]	<0.01	0.347	−119	[−202 −35]	**<0.01**
α	−29	[−214 157]	0.75	0.005	−73	[−214 67]	0.29
β	−29	[−189 130]	0.71	0.008	26	[−100 152]	0.67
Directional BSI	−86	[−238 66]	0.25	0.069	−142	[−244 −40]	**<0.01**
δ	−130	[−187 −73]	<0.01	0.542	−95	[−152 −38]	**<0.01**
θ	−124	[−195 −54]	<0.01	0.417	−99	[−153 −44]	**<0.01**
α	−21	[−139 97]	0.71	0.007	−103	[−188 −19]	**0.02**
β	23	[−68 114]	0.61	0.014	−27	[−102 47]	0.45

DAR: Delta Alpha power Ratio; BSI: Brain Symmetry Index; δ/θ/α/β: delta/theta/alpha/beta frequency band; B: regression coefficient; CI: confidence interval; R^2: R-squared; *Corrected for confounding factor: other neurological deficits (defined as the sum of the affected non-motor items of the NIHSS: visual impairment, facial palsy, ataxia, sensory, aphasia, dysarthria and extinction/inattention).

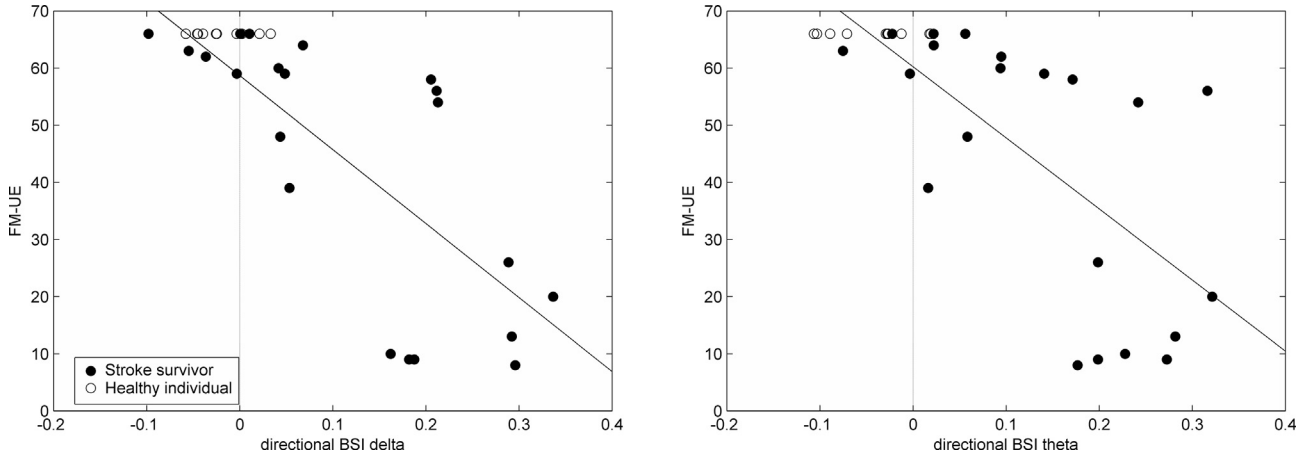


Fig. 1. Visualisation of the uncorrected association between directional Brain Symmetry Index (BSI_{dir}) of the delta or theta frequency band as independent variable and Fugl-Meyer motor assessment of the upper extremity (FM-UE) as dependent variable. Circles reflect healthy individuals. Filled dots reflect chronic stroke survivors. The dashed line reflects pure symmetry. For chronic stroke survivors a positive BSI_{dir} value refers to higher power in the affected hemisphere compared to the unaffected hemisphere, vice versa for negative values.

resting-state spectral density measures as DAR and BSI were compared between chronic stroke survivors and gender- and age-matched healthy individuals. Moreover, the association between these EEG parameters and the FM-UE in chronic stroke survivors was investigated. Significant differences between chronic stroke survivors and age- and gender-matched healthy individuals were found regarding BSI, but not for DAR. The asymmetry differences were most pronounced in the delta and theta frequency bands. In these frequency ranges significant negative associations were found between BSI and FM-UE.

4.1. DAR

In contrast to our hypothesis, DAR in chronic stroke survivors did not differ significantly from healthy individuals. This finding is incongruent with data from (sub) acute stroke survivors showing increased DAR values compared to healthy individuals (Sheorajpanday et al., 2009; Finnigan et al., 2016). However, Poryazova et al. (2015) showed an increased delta activity in early sub-acute stroke patients compared to matched controls, while this difference was no longer present in the late sub-acute phase. Therefore, we suggest that the discrepancies concerning the DAR may be caused by a difference in the time window of assessment post stroke, i.e., (sub) acute or chronic. In previous studies in (sub) acute stroke, DAR was shown predictive regarding recovery reflected by NIHSS (Finnigan et al., 2007; Finnigan and van Putten, 2013). However, in the current study conducted in the chronic phase, we did not find any association between DAR and FM-UE.

4.2. BSI

Our results support the hypothesis that chronic stroke survivors have a higher pairwise-derived BSI compared to healthy individuals. This asymmetry of brain activity power between hemispheres is more pronounced in chronic stroke survivors when compared to age- and gender-matched healthy controls. While existing literature particularly focuses on the (sub) acute phase, our study showed that this asymmetry may persist even in the chronic phase after stroke. This study shows no significant association of BSI with FM-UE when calculated over a range of 1–25 Hz when corrected for other neurological deficits.

4.3. BSI per frequency band

Brain lesions located in the cortex, white matter or both, have been shown to result in slower background rhythms. In awake adults increased slow wave activity in the delta and theta frequency band indicate cortical brain damage due to for example ischemia resulting from stroke, brain haemorrhage, tumours or traumatic injury (Britton et al., 2016). With increased severity of cortical brain damage the slowing becomes more pronounced (Britton et al., 2016). Analysing the BSI per frequency band revealed that the asymmetry is significantly more pronounced in chronic stroke survivors in the delta and theta band when compared to controls. However, this was not the case in the alpha or in the beta band. Moreover, the BSI in the delta and theta bands showed significant negative associations with FM-UE confirming that stroke survivors who show more asymmetry at the lower frequency bands are also more severely affected regarding the FM-UE. Our results suggest that parameters based on power spectral densities are of value in understanding impaired motor control in chronic stroke and emphasize the value of taking into account the frequency bands when calculating parameters based on power spectral densities.

4.4. Directional BSI

BSI_{dir} provides information on the directionality of asymmetry. In more severely affected stroke survivors, the lesioned hemisphere generated more power compared to the non-lesioned hemisphere, especially in the delta and theta frequency band. To the best of our knowledge, this is the first study using this specific parameter, which renders comparing the results with other studies difficult. Moreover, due to inter individual differences and the cross-sectional design of the study, we were not able to investigate whether the non-lesioned hemisphere was truly unaffected in patients with chronic stroke.

4.5. Presence of slow activity

Cortical deafferentation, which leads to loss of neuronal input, might be the cause of increased presence of low frequency oscillations (Schaul, 1998). Slow waves, like activity in the delta and theta frequency bands, can be observed in different neurological disorders. Since there is no specific cause of these low frequency oscillations, its presence has been considered to reflect general cerebral dysfunction of the brain (Andraus and Alves-Leon, 2011). In stroke survivors, it has been shown to be indicative of a localized structural lesion (Schaul, 1998). Several studies showed that this low frequency content is of significant value regarding prognosis of functioning in this population (e.g. Finnigan and Van Putten, 2013). The current study shows that low frequency content is of significant value in the chronic phase as well.

4.6. Selective motor control

During resting state the brain shows active networks in which both hemispheres interact. Reorganization after stroke can result in frequency shifts and shifts in neural activity of anatomically related cortical areas. Therefore, resting state activity might become more lateralized due to stroke. In this way, altered connectivity in the cortex due to stroke may result in an EEG power asymmetry between the affected and unaffected hemisphere. It has been shown that changed cortical resting state activity is related to motor dysfunction during movements (Carter et al., 2012). Moreover, activity in the sensorimotor areas facilitates selective motor control via the corticospinal tract (Cahill-Rowley and Rose, 2014). Disorganization of these sensorimotor areas has been shown to be involved in impairments of selective motor control (Yao et al., 2009). Therefore, although speculative, this may be a possible way in which cortical damage, expressed by power spectral density-based EEG parameters, causes deficits in selective motor control.

4.7. Limitations and further directions

In this cross-sectional study, a comparatively small number of chronic stroke survivors was investigated. Besides, MRI data was only used to obtain lesion location, lesion volume was not calculated. Current prediction models of motor function recovery post stroke are typically based on clinical measures like FM-UE. They do not predict the outcome properly in all cases and the underlying mechanisms of recovery are still poorly understood. Biomarkers that reflect underlying mechanisms are currently lacking, but can be particularly useful to determine which patients should receive an intervention at what moment in time (Boyd et al., 2017). Therefore, we recommend to investigate the longitudinal dynamics between power spectral density-based EEG parameters and upper limb recovery, since this may provide insight in the time-course of underlying processes of recovery and may improve prediction models (Ward, 2017). Based on the findings of the current study,

we recommend considering DAR, low frequency asymmetry measures and directional asymmetry measures. Acknowledging that spontaneous neurological recovery mainly defines the pattern of FM-UE improvements in the first eight weeks post stroke (van Kordelaar et al., 2013; Duncan et al., 1992; Kwakkel et al., 2006), we further recommend to perform intensive repeated measurement designs with clinical and EEG measurements at fixed moments early post stroke (Bernhardt et al., 2017).

4.8. Conclusions

Cortical asymmetry in resting-state EEG, expressed by the pairwise-derived BSI, is increased in chronic stroke survivors especially in the lower frequency bands. Higher asymmetry in the delta and theta band is associated with poorer motor function. This implies that asymmetry in the delta and theta frequency band may be a useful biomarker for the neural state after stroke. We conclude that assessing the asymmetry in future stroke-related recovery studies, specifically in delta and theta power distributions, may provide more insight in the relation between reorganization of the cortex and motor recovery.

Declaration of interest

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

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2019.01.007.

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