Are early measured resting-state EEG parameters predictive for upper limb motor impairment six months poststroke?

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Abstract

Objectives: Investigate whether resting-state EEG parameters recorded early poststroke can predict upper extremity motor impairment reflected by the Fugl-Meyer motor score (FM-UE) after six months, and whether they have prognostic value in addition to FM-UE at baseline.

Methods: Quantitative EEG parameters delta/alpha ratio (DAR), brain symmetry index (BSI) and directional BSI (BSIdir) were derived from 62-channel resting-state EEG recordings in 39 adults within three weeks after a first-ever ischemic hemispheric stroke. FM-UE scores were acquired within three weeks (FM-UEbaseline) and at 26 weeks poststroke (FM-UEw26). Linear regression analyses were performed using a forward selection procedure to predict FM-UEw26.

Results: BSI calculated over the theta band (BSItheta) (β = -0.40; p = 0.013) was the strongest EEG-based predictor regarding FM-UEw26. BSItheta (β = -0.27; p = 0.006) remained a significant predictor when added to a regression model including FM-UEbaseline, increasing explained variance from 61.5% to 68.1%.

Conclusion: Higher BSItheta values, reflecting more power asymmetry over the hemispheres, predict more upper limb motor impairment six months after stroke. Moreover, BSItheta shows additive prognostic value regarding FM-UEw26 next to FM-UEbaseline scores, and thereby contains unique information regarding upper extremity motor recovery.

Significance: To our knowledge, we are the first to show that resting-state EEG parameters can serve as prognostic biomarkers of stroke recovery, in addition to FM-UEbaseline scores.

1. Introduction

Stroke is a major cause of adult disability worldwide (Sacco et al., 2013). In the early phase, about 80% of stroke survivors suffer from motor impairments of the upper extremity (Langhorne et al.,...
Subjects may range from non-recoverers to excellent recoverers, studies showed that the variation in degree of recovery between months after stroke, is the FM-UE scores at baseline predictors of chronic motor impairment, reflected by the FM-UE six 1951). Several studies showed that one of the best early phase pre- tions when performing selective, dissociated movements (Twitchell, 1951). Several studies showed that one of the best early phase predictors of chronic motor impairment, reflected by the FM-UE six months after stroke, is the FM-UE scores at baseline (Prabhakaran et al., 2008; Winters et al., 2015). However, recent studies showed that the variation in degree of recovery between subjects may range from non-recoverers to excellent recoverers, suggesting that FM-UE measured at baseline (FM-UEbaseline) in itself may not be an optimal predictor (Prabhakaran et al., 2008; Winters et al., 2015; Vliet et al., 2020). As noted by the Stroke Recovery and Rehabilitation Roundtable (SRRR) task force, there is an urgent need for complementary prognostic biomarkers in addition to clinical assessments to optimize the accuracy of current prediction models for spontaneous motor recovery (Boyd et al., 2017; Ward, 2017). This is particularly important as early post-stroke clinical assessments may not be able to distinguish patients who will show spontaneous upper limb motor recovery from those who will not (Vliet et al., 2020).

Parameters derived using structural imaging techniques showed that corticospinal tract (CST) integrity has predictive value for motor recovery (Puig et al., 2017; Rondina et al., 2017; Lin et al., 2019). The predictive value of motor evoked potentials and asymmetry in fractional anisotropy of the posterior limbs of the internal capsules also indicates a role for the CST regarding motor recovery (Byblow et al., 2015). Next to these structural imaging characteristics, potential biomarkers that might be associated with motor outcome include derivatives of cortical activity, which can be recorded using electroencephalography (EEG) (Ward, 2017). The level of cortical deficits after stroke may be quantified by resting-state EEG, as altered resting-state cortical activity has been associated with motor dysfunction (Carter et al., 2012; Guggisberg et al., 2019). Resting-state EEG recording is specifically suitable for the stroke population early after onset, since it is portable, non-invasive and does not require voluntary motor performance with the paretic upper limb.

Hemispheric stroke has been associated with altered low-frequency oscillations in the delta and theta bands (van Putten and Tavy, 2004; Andraus and Alves-Leon, 2011; Finngian and van Putten, 2013; Britton et al., 2016), whereas unaltered alpha activity seems to be associated with healthy brain activity (Bazanova, 2012). A combination of these spectral characteristics can be expressed by the delta/alpha ratio (DAR). This ratio may more sensitively reflect the severity of neurological deficits compared to the individual spectral components, as, for instance, delta activity may increase with or without decreased alpha activity. Unilateral stroke may also affect the activity of the cortical areas involved through modified spectral power distributions over the hemispheres. This power asymmetry can be quantified via the pairwise-derived brain symmetry index (BSI) (Sheorajpanday et al., 2009) and directional BSI (BSIdir) (Saes et al., 2019).

Quantitative resting-state EEG parameters such as DAR and BSI, measured early poststroke, are predictors of future global neurological deficits reflected by the National Institutes of Health Stroke Scale (NIHSS) and degree of dependency assessed with the modified Rankin Scale (mRS) (Finnigan et al., 2007; Sheorajpanday et al., 2011; Finngian and van Putten, 2013; Bentes et al., 2018; Doerrfuss et al., 2020). Furthermore, recent analyses showed that BSI calculated over the delta frequency band (BSIdelta) was longitudinally associated with FM-UE, whereas DAR, DAR of the affected hemisphere (DARaffected), BSI, BSIdir over the delta (BSIdelta) and theta band (BSIdirtheta), were longitudinally associated with NIHSS (Saes et al., 2020). However, the potential of EEG parameters to serve as additional prognostic biomarker when combined with clinical scores regarding upper limb motor recovery poststroke remains unclear (Doerrfuss et al., 2020).

The first objective of the current analysis of the prospective cohort study named 4D-EEG was to investigate whether early measured resting-state EEG parameters have predictive value regarding motor impairment of the paretic upper limb, as reflected by FM-UE, six months after a first-ever ischemic stroke. We expected this to be true, especially for the BSI and BSIdir over the low frequency bands which were previously found to be longitudinally associated with FM-UE (Saes et al., 2020). Our second aim was to investigate whether these resting-state EEG parameters have prognostic value in addition to FM-UE measured at baseline.

2. Methods

2.1. Participants

All patients who were admitted to the stroke units of six participating hospitals between June 2015 and June 2017 were potentially eligible for participation. The inclusion criteria were: (1) first-ever ischemic stroke according to CT or MRI scan; (2) less than three weeks poststroke; (3) upper limb paresis (NIHSS 5a/b > 0); (4) ≥ 18 years of age; and (5) having provided written informed consent. Exclusion criteria were: (1) upper extremity orthopedic limitations prior to stroke onset; (2) recurrent stroke; (3) severe cognitive problems, i.e. Mini Mental State Examination score < 18; (4) other neurological deceases; and (5) using medication which is likely to affect neuronal oscillations. The study was registered at the Netherlands Trial Register (NTR4421), approved by the Medical Ethics Committee of the VU University Medical Center, Amsterdam, The Netherlands (4D-EEG: NL47079.029.14) and carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki, 2013) (World Medical Association, 2013). Analyses were performed on longitudinal data of 39 participants, which were also used for analyses in Saes et al. (2020). There was no overlap regarding participants included in Saes et al. (2019). All participants received usual care according to the Dutch stroke guidelines for physical therapy (Veerbeek et al., 2014).

2.2. Procedures

The baseline measurement involved an EEG recording and a clinical assessment performed on consecutive days, as soon after stroke onset as feasible, but at least within the first three weeks. EEG recordings were performed in a specially equipped van (Saes et al., 2020). This provided the opportunity to visit patients at their place of residence, to limit their burden and ensure standardization. FM-UE was performed as part of the baseline clinical assessment (FM-UEbaseline) and repeated at 26 weeks poststroke (FM-UE26w).

2.3. Electroencephalography

High-density 62-channel EEG was recorded using an actively shielded EEG cap with electrode placement according to the international 10–20 system at a sampling rate of 2048 Hz (Ag/AgCl electrodes and REFA multichannel amplifier, TMSI, Oldenzaal, The
Netherlands, with ASA acquisition software, ANT software BV, The Netherlands). Resting-state EEG with eyes open was acquired while subjects were seated and focused their eyes on a dot displayed on a screen for one minute. Five 1-minute trials were recorded, with sufficient rest in between. Electrode impedances were kept below 20 kΩ. EEG signals were online referenced to average. During the EEG recording, muscle relaxation of the arms was monitored using bipolar Ag/AgCl electrodes to detect muscle activity of the m. extensor carpi radialis and m. flexor carpi radialis of both arms.

2.3.1. Pre-processing

Offline analysis was conducted using Matlab (R2012a, The Mathworks, Natick, MA, USA) in combination with the FieldTrip toolbox for EEG/MEG analysis (Oostenveld et al., 2011). EEG signals were filtered using a 4th-order bi-directional high-pass Butterworth filter with a cut-off at 0.5 Hz. A notch filter around 50, 100 and 150 Hz with a bandwidth of 1 Hz was used to reduce power-line artefacts, followed by a low-pass filter at 130 Hz. Channels which showed no data or very poor data quality were rejected and interpolated as the weighted average of the surrounding electrodes, followed by re-referencing to the remaining average. On average, 0.17 electrodes were interpolated per measurement. Eye-blinks and muscle activity artefacts were removed using independent component analysis based on visual inspection of the components’ waveforms, power spectrum and topographic distributions. On average 2.9 components were removed per measurement. Remaining artefacts were removed during a second round of visual inspection. Modified periodograms with a Hanning window with size equal to the epoch length served as proxies of the spectral power density per channel.

2.3.2. Quantitative resting-state EEG parameters

2.3.2.1. Delta/alpha ratio. Hemispheric stroke has been associated with increased low frequency oscillations in the delta and theta band (van Putten and Tavy, 2004; Andraus and Alves-Leon, 2011; Finnigan and van Putten, 2013; Britton et al., 2016). On the other hand, unaltered alpha activity has been associated with healthy brain activity (Bazanova, 2012). The delta/alpha ratio (DAR) combines these spectral characteristics and was defined as the ratio between the mean delta power (1–4 Hz) and the mean alpha power (8–12 Hz). For every channel c the power of the delta and alpha frequency bands (f = 1,...,4 Hz and f = 8,...,12 Hz, respectively) was determined as the mean of the spectral power $P_{c}(f)$ over this range. The DAR was computed as

$$\text{DAR}_{c} = \frac{\langle P_{c}(f) \rangle_{f=1...4Hz}}{\langle P_{c}(f) \rangle_{f=8...12Hz}} \quad (1)$$

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

$$\text{DAR} = \frac{1}{N} \sum_{c=1}^{N} \text{DAR}_{c} \quad (2)$$

In addition to the assessment over the whole brain, DAR was also determined over the affected (DAR_{AH}) and unaffected hemisphere (DAR_{NH}).

3. Brain symmetry index

The BSI represents the spectral power distribution asymmetry over the hemispheres, which may be affected due to unilateral stroke altering cortical activity. BSI was defined as the absolute pairwise normalized difference in spectral power between the homologous channels over the left $c_{L}$ and right $c_{R}$ hemisphere. The difference was averaged over a range from 1 to 25 Hz (adapted from Sheeroajipanday et al., 2009) according to

$$\text{BSI}_{cp} = \frac{|P_{cL}(f) - P_{cR}(f)|}{P_{cL}(f) + P_{cR}(f)} \quad (3)$$

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

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

BSI values theoretically range from 0 to 1, indicating maximal symmetry and maximal asymmetry, respectively. In (3) and (4), electrodes of the mid-line were excluded since they do not form channel-pairs. In our earlier study, we showed the relevance of the lower frequency bands for the stroke population (Saes et al., 2019). Therefore, in addition to the estimates over the entire 1–25 Hz range, BSI was also determined separately for the delta (1–4 Hz) and theta (4–8 Hz) frequency bands (BSI_{delta} and BSI_{theta}).

To account for the direction of the asymmetry, we also computed the directional BSI (BSIdir) (Saes et al., 2019). The BSIdir disregards the absolute value of the numerator of the BSI calculation shown in (3). The sign of BSIdir was chosen such that values between 0 and 1 reflected greater cortical power in the affected hemisphere compared to the unaffected hemisphere, and vice versa for values between −1 and 0. Also BSIdir was determined separately for the delta (BSIdir_{delta}) and theta (BSIdir_{theta}) frequency band.

3.1. Clinical measures

FM-UE (range [0–66]) is a valid and reliable clinical test reflecting motor impairment after stroke (Gladstone et al., 2002). Additional clinical assessments for subject characterization included NIHSS, Action Research Arm Test (ARAT), Erasmus MC modification of the Nottingham Sensory Assessment of the upper extremity (EmNSA), Motricity Index of the Upper/Lower Extremity (MI-UE/MI-LE), Edinburgh Handedness Inventory and Bamford classification.

3.2. Statistics

A forward selection procedure was used to identify the strongest predictor of FM-UE_{w26} based on quantitative resting-state EEG. Investigated EEG parameters concerned: DAR, DAR_{AH}, DAR_{NH}, BSI, BSIdir_{delta}, BSIdir_{theta}, BSIdir_{delta}, and BSIdir_{theta}.

Subsequently, a stepwise forward selection procedure with FM-UE_{baseline} as base model, was used to find the EEG parameter which has the most added value. The F-test was used to check whether adding a quantitative resting-state EEG parameter significantly increased the explained variance.

All statistical analyses were conducted using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). For each model, the distribution of residuals was tested for normality by inspecting histograms and Q-Q plots. As is common in prediction models, the significance level of covariates was set to $\alpha < 0.05$.

4. Results

4.1. Participants

A total of 2095 patients were screened, 55 of whom were eligible and willing to participate in this longitudinal observational cohort study. Thirty-nine patients completed the EEG recording at baseline and the clinical assessments at baseline and 26 weeks poststroke, and were included in the analyses. A flowchart of
screening, inclusion and drop-outs is depicted in Fig. 1. The EEG recording was performed at 12.3 ± 5.8 days (mean ± SD) post-stroke. Clinical assessments were performed at 11.6 ± 5.3 and 185.2 ± 20.0 days post-stroke, referred to as baseline and w26, respectively. In the present study, the number of days between stroke onset and the baseline clinical measurement or EEG recording was not significantly correlated with FM-UEbaseline (r(37) = −0.206, p = 0.21 and r(37) = −0.273, p = 0.09; respectively). Patient characteristics are summarized in Table 1. A complete overview of the data can be found in Supplementary Table S1.

4.2. EEG-derived predictors of FM-UEw26

The forward selection procedure revealed that BSItheta is the strongest predictor of the investigated EEG parameters with respect to FM-UEw26 scores (B = −156.81, 95%-CI = [−277.93 to −35.70], p = 0.013, β = −0.40, R² = 0.16) (Table 2). Hereby, a higher BSItheta predicts a lower FM-UEw26.

4.3. EEG parameters with additive prognostic value in addition to FM-UEbaseline

The forward selection procedure revealed that BSItheta was the EEG parameter with most predictive value in addition to FM-UEbaseline (B = −108.09, 95%-CI = [−182.74 to −33.44], p = 0.006, β = −0.27, R²adj = 0.68), where a higher BSItheta value predicts a lower FM-UEw26 (Table 3). FM-UEbaseline remained significant (p < 0.001; Table 3). FM-UEbaseline alone explained 61.5% of the variance of DAR and BSI, and FM-UEbaseline remained significant (p < 0.001; Table 3). FM-UEbaseline alone explained 61.5% of the variance of DAR (R² = 0.615, F(1,37) = 61.7, p < 0.001; Table 3). Adding BSItheta increased the explained variance of the prediction model significantly to 68.1% (R²adj = 0.681, F-change(1,36) = 8.6, p = 0.006; Table 3).

5. Discussion

We investigated whether early measured resting-state EEG parameters have prognostic value regarding upper extremity motor impairment at six months poststroke in 39 patients. From the investigated quantitative resting-state EEG parameters, hemispheric power asymmetry in the theta band (BSItheta) was the strongest prognostic biomarker of FM-UEw26. A higher BSItheta, reflecting more asymmetry between hemispheres in the theta band, predicts a lower FM-UEw26. Moreover, BSItheta showed prognostic value in addition to baseline FM-UE alone and increased the explained variance from 61.5% to 68.1%. This reveals that BSItheta contains unique information compared to upper extremity motor scores at baseline regarding upper extremity motor impairment at six months, and therefore has potential to serve as additive prognostic biomarker of stroke recovery.

The present study is the first to investigate the prognostic value of quantitative resting-state EEG parameters (DAR and BSI, and variations thereof) measured early poststroke regarding upper extremity motor impairment after six months, as reflected by FM-UE. Earlier studies showed that these EEG parameters could serve as predictors of global neurological impairment (NIHSS) and degree of dependency regarding daily activities (mRS) post-stroke (Sheorajpanday et al., 2010, 2011; Bentes et al., 2018; Doerrfuss et al., 2020).

In contrast to BSI, DAR was not a predictor of the motor function of the upper extremity at 26 weeks poststroke, although earlier studies did show prognostic value of DAR regarding global neurological impairments reflected by NIHSS at 30 days poststroke (Finnigan et al., 2007; Finnigan and van Putten, 2013) or negative functional outcome reflected by mRS > 3 at 12 months poststroke (Bentes et al., 2018). The absence of predictive value of DAR regarding FM-UE is in line with our earlier analyses, in which we showed a longitudinal association of DAR with NIHSS, but not with FM-UE (Saes et al., 2020). Furthermore, Butz et al. (2004) showed no relation between clinical symptoms and increased delta activity near the lesion measured between one and fourteen days poststroke (Butz et al., 2004). DAR was previously found to be a predictor of NIHSS when assessed within 48 hours after stroke onset, and DAR was shown to be a predictor of negative functional outcome (mRS ≥ 3) when assessed within 72 hours, while the mean post-stroke measurement time in the current study was 12.3 days (Finnigan et al., 2007; Bentes et al., 2018). It has been suggested that DAR decreases (i.e. normalizes) between 24 and 48 hours poststroke (Finnigan et al., 2007, 2016). Therefore, although speculative, when DAR may serve as prognostic biomarker, this may be restricted to the very early stage poststroke.

The present results show that BSItheta has added value in predicting upper extremity motor impairment at six months post stroke compared to the FM-UEbaseline score alone. Previously, BSI was shown to be a predictor of negative functional outcome (mRS ≥ 3), but not when corrected for other clinical scores (Bentes et al., 2018). However, the BSI over the low frequency bands was not investigated. BSItheta may have the potential to serve as additive prognostic biomarker of motor recovery in addition to clinical measures. Our findings suggest that EEG data contains unique information regarding stroke severity, possibly as a reflection of cortical network integrity, which is required for behavioral recovery. The fact that this added value originates especially from low-frequency oscillations, is in line with the suggestion that such activity is related with reorganization. Low-frequency cortical activity may be the result of partial deafferentation of the cortex caused by a lesion which damaged cortico-cortical connections (Gloor et al., 1977; Butz et al., 2004). Furthermore, synchronous neuronal activity in the low-frequency range has been related with...
**Table 1**

Patient characteristics.

| Demographics and clinical scores | Baseline | 26 weeks poststroke |
|----------------------------------|----------|---------------------|
| Time post stroke (days), clinical assessment | 11.6 (5.3) | 185.2 (20.0) |
| Time post stroke (days), EEG recording | 12.3 (5.8) | |
| Age (years) | 67.3 (11.4) | |
| Gender (male/female) | 23/16 | |
| Affected hemisphere (left/right) | 18/21 | |
| Hand dominance (left/right) | 5/34 | |
| Bamford classification | 20/14/5 | |
| FM-UE* | 21 | (7–42) |
| NIHSS* | 5 | (4–8) |
| EmNSA* | 38 | (34.5–40) |
| MI-UE* | 39 | (12.5–71) |
| MI-UE* | 53 | (28–73.5) |
| ARAT* | 3.5 | (0–32) |

Demographics and clinical scores of all patients included in the analysis (N = 39) at baseline and 26 weeks poststroke. *Median (interquartile range). Abbreviations: Time post stroke, days elapsed between stroke onset and baseline measurement; N, number of participants; SD, standard deviation; LACI, lacunar anterior circular infarct; PACI, partial anterior circular infarct; TACI, total anterior circular infarct; FM-UE, Fugl-Meyer motor assessment of the upper extremity; NIHSS, National Institutes of Health Stroke Scale; EmNSA, Erasmus modification of the Nottingham Sensory Assessment of the upper extremity; MI–UE/LE, Motricity Index of the Upper/Lower Extremity; ARAT, Action Research Arm Test.

**Table 2**

Regression coefficients of early measured resting-state EEG parameters to predict FM–UE score at six months poststroke.

| EEG parameter | FM-UEw26 | DAR | -0.63 | [−3.76 2.50] | 0.685 | −0.07 | 0.00 |
|---------------|----------|-----|-------|----------------|-------|--------|------|
| DARalpha | -0.90 | [−3.11 1.32] | 0.418 | −0.13 | 0.02 |
| DARrest | 1.08 | [−3.51 5.68] | 0.636 | 0.08 | 0.01 |
| BSI | -183.88 | [−332.90–34.87] | 0.017 | −0.38 | 0.15 |
| BSIalpha | -98.19 | [−198.43 2.05] | 0.055 | −0.31 | 0.16 |
| BSIdeltatheta | -156.81 | [−277.93–35.70] | 0.013 | −0.40 | 0.16 |
| BSIdir | 27.44 | [−3–80.3 137.88] | 0.618 | 0.08 | 0.01 |
| BSIdiralpha | -58.09 | [−116–0.70] | 0.053 | −0.31 | 0.10 |
| BSIdirdeltatheta | -53.33 | [−122–22 15.56] | 0.125 | −0.25 | 0.06 |

Dependent variable: FM-UEw26. Abbreviations: FM-UEw26, Fugl-Meyer motor assessment of the upper extremity at 26 weeks poststroke; DAR, delta/alpha ratio; AH/UH, affected/unaffected hemisphere; BSI, brain symmetry index; BSIdir, directional BSI; delta/theta, calculated over the delta (1–4 Hz) or theta (4–8 Hz) frequency band; B, regression coefficient; 95%-CI, 95%-confidence interval; p, probability value; significance level was set to < 0.05, significant p-values are displayed in Bold font; B, standardized beta; R2, explained variance.

**Table 3**

Regression coefficients of early measured EEG parameters in addition to FM–UE baseline scores to predict FM–UE score at six months poststroke.

| EEG parameter | FM-UEbaseline | DAR | -0.01 | [−1.97 1.95] | 0.991 | <0.001 | 0.79 |
|---------------|---------------|-----|-------|----------------|-------|--------|------|
| DARalpha | -0.38 | [−1.77 1.01] | 0.584 | -0.06 | 0.90 | 0.607 | 0.31 |
| DARrest | 1.41 | [−1–4 2.43] | 0.320 | 0.10 | 0.91 | 0.615 | 1.02 |
| BSI | -104.22 | [−200.67–7.77] | 0.035 | 0.21 | 0.85 | 0.651 | 4.80 |
| BSIalpha | -76.63 | [−137.10 16.16] | 0.014 | 0.24 | 0.88 | 0.665 | 6.61 |
| BSIdeltatheta | -108.09 | [−182.73–33.44] | 0.006 | 0.27 | 0.85 | 0.681 | 8.62 |
| BSIdir | 36.05 | [−31.77 103.87] | 0.283 | 0.11 | 0.91 | 0.616 | 1.16 |
| BSIdirdeltatheta | -24.35 | [−63.09 14.40] | 0.211 | 0.13 | 0.87 | 0.621 | 1.63 |
| BSIdirdeltatheta | -33.41 | [−76.49 9.68] | 0.125 | 0.16 | 0.88 | 0.630 | 2.47 |

Dependent variable: FM-UEw26. Abbreviations: FM-UEbaseline, Fugl-Meyer motor assessment of the upper extremity measured within three weeks poststroke; FM–UEw26, FM–UE at 26 weeks poststroke; DAR, delta/alpha ratio; AH/UH, affected/unaffected hemisphere; BSI, brain symmetry index; BSIdir, directional BSI; delta/theta, calculated over the delta (1–4 Hz) or theta (4–8 Hz) frequency band; B, regression coefficient; 95%-CI, 95%-confidence interval; p, probability value; significance level was set to < 0.05, significant p-values are displayed in Bold font; B, standardized beta of the particular covariate; R2adj, adjusted R-squared, variance explained by the model; Fchange, change of F-statistic relative to the prediction model based on FM–UEbaseline only; pchange, probability value of F-change.

Axonal sprouting after ischemic lesions in rats (Carmichael and Chesselet, 2002). Therefore, it has been suggested that increased low-frequency activity may be related with reorganization after stroke (Butz et al., 2004). BSI showed to have prognostic value in contrast to BSIdeltatheta. This suggests that not just the affected hemisphere shows increased theta power compared to the less-affected hemisphere but also vice-versa. Therefore, compared to BSIdeltatheta,
BSIbeta might be a better reflection of neuronal damage with predictive value.

5.1. Limitations

Despite using a specially equipped van that allowed to visit patients at their place of residence to limit their burden (Saes et al., 2020), a number of patients (14 out of 55) dropped out during this longitudinal observational study. The measurement protocol presented here was part of a larger serially conducted protocol of the 4D-EEG study, and the resting-state condition recording took only a few minutes of the quite extensive EEG recording protocol. The protocol as actually performed was adjusted for each patient to ensure feasibility and prevent overloading. However, five patients experienced the measurements as too exhausting, especially regarding the combination of their usual care and participating in research. Generalizability was analyzed by performing a cross-validation using a leave-one-out procedure, which showed that the standard error of the estimate increased by only 3.4% compared to the model based on all data. External cross-validation using an independent dataset should be performed to confirm presented findings. The maximum NIHSS score observed at inclusion was 15, indicating that our sample does not contain severely affected patients and may suffer from sampling bias. Nevertheless, we see a large variety in upper extremity motor deficits reflected by FM-UE, which was the focus of our study. Inclusion of severely affected stroke patients would most likely have increased the number of patients with low FM-UE scores. Since in those patients FM-UEbaseline may be limitedly informative regarding the prediction of their recovery (Van der Vliet et al., 2020), we expect the additive predictive value of EEG to increase. This requires further investigation. Methodological procedures resulted in a time delay of about twelve days between stroke onset and the first measurement. Therefore, we could not quantify possible changes regarding neurological deficits in the first days after stroke onset. In addition, the present study focused on DAR and BSI (and variations thereof), while other quantitative EEG parameters, such as delta-theta/alpha-beta ratio or relative powers per frequency band, might have prognostic value as well (Bentes et al., 2018). Furthermore, in the current study MRI data was unavailable for a large proportion of the patients. Finally, the present study was focused on FM-UE, which is the clinical assessment closest related with neurological impairment. However, BSIbeta also showed potential for prediction of upper limb capacity reflected by ARAT as outcome measure, emphasizing its robustness (Supplementary Tables S2 and S3).

5.2. Future directions

Prediction modeling for the identification of patients who show recovery poststroke is of high interest in the current literature. A recently proposed mixture model classifies stroke patients into five recovery groups based on initial FM-UE scores and their recovery pattern (Vliet et al., 2020). Moderately and severely affected patients in particular were shown to be often misclassified and may benefit from additional prognostic biomarkers (Winters et al., 2015; Vliet et al., 2020). It remains to be investigated whether quantitative resting-state EEG parameters improve the accuracy of the mixture model, and thereby improve the identification of severely affected patients who will show recovery. Allowing to take early changes into account, the first EEG recording should preferably be performed within the first days after stroke and repeated more frequently within the first weeks.

Second, the current study only concerned the recovery of FM-UE scores, which is assumed to be a clinical measure most closely related to behavioral restitution. However, it is known that FM-UE scores suffer from ceiling effects after three months poststroke (Gladstone et al., 2002). Kinematic or kinetic performance assays, such as selective elbow extension during restrained reaching, finger indviduation or pinch and grip strength, may be more fine-grained and responsive to behavioral restitution as a reflection of true neurological repair (Kwakkel et al., 2019).

Furthermore, the additive prognostic value of very early derived EEG parameters (<72 hours poststroke) above clinical measures has still to be established. Limiting the number of electrodes lowers the burden of patients and increases feasibility of performing EEG recordings in the acute phase. For example, a previous study showed that quantitative EEG parameters derived from only four electrodes have prognostic value regarding cognitive functioning (Schleiger et al., 2014). The minimum number and exact location of the EEG electrodes to obtain data with added value regarding motor recovery in the very early phase has yet to be investigated.

Finally, besides quantitative resting-state EEG parameters, several other parameters can be derived from EEG data, which should be considered. An example is the dynamic signal propagation between active cortical sources during a sensory stimulation task, derived from a combination of EEG, MRI and diffusion MRI data (Filatova et al., 2018). This technique enables the association between the quality of task-specific signal propagation and functional recovery to be investigated serially during motor recovery after stroke. Furthermore, a MEG study in stroke patients showed that reduced movement-related beta desynchronization is related to the level of motor impairment (Rossiter et al., 2014). Also EEG parameters reflecting the quality of functional network organization within and between hemispheres might be of interest for understanding which patients show recovery after stroke and which do not (Nicolo et al., 2015; Guggisberg et al., 2019). For example, inter-regional synchronization of neural oscillations in the first weeks after stroke has been associated with improvement of motor function (Nicolo et al., 2015). It remains to be investigated how these parameters develop longitudinally within the different subgroups of proportional recovery (Vliet et al., 2020) and whether they may serve as prognostic biomarkers for the outcome at six months poststroke.

Declaration of Competing Interest

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Appendix A. Supplementary material

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