Low-Frequency Brain Oscillations Track Motor Recovery in Human Stroke

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Objective: The majority of patients with stroke survive the acute episode and live with enduring disability. Effective therapies to support recovery of motor function after stroke are yet to be developed. Key to this development is the identification of neurophysiologic signals that mark recovery and are suitable and susceptible to interventional therapies. Movement preparatory low-frequency oscillations (LFOs) play a key role in cortical control of movement. Recent animal data point to a mechanistic role of motor cortical LFOs in stroke motor deficits and demonstrate neuromodulation intervention with therapeutic benefit. Their relevance in human stroke pathophysiology is unknown.

Methods: We studied the relationship between movement-preparatory LFOs during the performance of a visuomotor grip task and motor function in a longitudinal (<5 days, 1 and 3 months) cohort study of 33 patients with motor stroke and in 19 healthy volunteers.

Results: Acute stroke–lesioned brains fail to generate the LFO signal. Whereas in healthy humans, a transient occurrence of LFOs preceded movement onset at predominantly contralateral frontoparietal motor regions, recordings in patients revealed that movement-preparatory LFOs were substantially diminished to a level of 38% after acute stroke. LFOs progressively increased at 1 and 3 months. This re-emergence closely tracked the recovery of motor function across several movement qualities including grip strength, fine motor skills, and synergies and was frequency band specific.

Interpretation: Our results provide the first human evidence for a link between movement-preparatory LFOs and functional recovery after stroke, promoting their relevance for movement control. These results suggest that it may be interesting to explore targeted, LFOs-restorative brain stimulation therapy in human stroke patients.

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Most patients with stroke survive the acute episode and live with enduring disability. Upper limb paresis in particular is one of the most common long-term disabilities after stroke1 and constitutes one, if not the most limiting factor in the reintegration to daily life2 and return to work.3,4 Effective therapies to improve motor function after stroke are yet to be developed. Therapies targeting restorative processes encompass brain stimulation techniques. Advancement to clinical practice has so far been unsuccessful,5–8 which is partly attributable to poorly understood links between stimulation mechanism and individual pathophysiology.9,10 An emerging new avenue of brain stimulation strongly relies on a close link between the stimulation effects and pathophysiology and follows the rationale of replacing pathophysiologically missing signals via on-demand electric stimulation, thereby normalizing neural coding in downstream brain regions.9,11,12 The therapeutic potential of targeted neuromodulatory stimulation for restoration of human motor control was recently evidenced by 3 breakthrough studies in the treatment of paralysis after spinal cord injury.13–15 For stroke, an on-demand neurostimulation was recently shown to improve...
skillful reaching and grasping after stroke in rodents. Movement-related low-frequency oscillations (LFOs) in the motor cortex served as the stimulation target. These are brief periods of oscillatory activity in the delta and lower theta band that appear at motor cortical areas before and around movement onset and in animal recordings were shown to contain rich information about movement direction, velocity, and trajectory as well as on grip types. Previous studies have proven the existence of LFOs also in human motor control, but the temporospatial pattern of LFO generation and propagation during movement preparation in humans is not well known. Importantly, whether LFOs are similarly a hallmark of human stroke pathophysiology and recovery is unknown, but essential for translational attempts of the stimulation paradigm successful in rodents. Do humans show a comparable cortical pathophysiology regarding movement-related LFOs, that is, are movement-related LFOs abolished after an acute motor stroke and likewise re-emerge with time after stroke? Is this re-emergence relevant for motor recovery?

We conducted a longitudinal study in patients recovering from a hand motor deficit after stroke, measuring cortical electric fields via electroencephalography (EEG) during the performance of a grip force task (Fig 1A). Thirty-three patients were measured in the acute (3–5 days poststroke), early subacute (1 month), and late subacute stage (3 months) and clinically characterized with a comprehensive testing battery. To understand temporospatial patterns of movement-related LFOs in the healthy and diseased brain, 19 age-matched volunteers performing the same grip force task were likewise recorded.

Subjects and Methods

Study Protocol

Acute stroke patients (≤5 days) were included according to the following criteria: first ever ischemic stroke causing a motor deficit involving hand function, absence of higher cognitive deficits like aphasia or hemianopia that prevented patients from giving written informed consent or from comprehending visual task instructions, modified ranking scale ≤5 and absence of disabling other comorbidities, no past seizure, and no contraindications for magnetic resonance imaging (MRI; Fig 2B). Sixty-one patients passed the eligibility criteria at the acute stage and were included in the study. Longitudinal measurements at 3 timepoints after stroke (3–5 days, 1 month, 3 months) included standardized clinical testing (Fugl–Meyer Assessment upper limb section [UEFMA], Nine-Hole Peg Test performance value [NHP], whole hand grip force, neurologic examination), structural MRI, and task-related EEG. Longitudinal task-related recordings at all timepoints were available from 33 patients (age = 64.1 ± 2.2 mean ± standard error [SE] years, 12 females, 1 left-handed). See the Supplementary Table for stroke demographics and clinical measurements at each timepoint. An age-matched control group (n = 19, age = 64.8 ± 2.6 years, 9 females, 1 left-handed) was subjected to the same measurements. The study protocol conforms to the Code of Ethics of the World Medical Association (Declaration of Helsinki) and received approval from the local ethics committee of the Medical Association of Hamburg, Germany. Patient’s informed consent was obtained accordingly.

Motor Task

Participants performed an isometric visually guided whole hand grip task with the paretic (in control participants the side was counterbalanced accordingly) hand, as described in Figure 1A, legend to Figure 1, and previously. We compared 2 conditions of varying target grip force, one keeping the force constant across the group (constant output of 5kg) and the other keeping the task effort constant across the group (constant effort of 20% maximum voluntary contraction). Each condition was recorded with 20 repetitions of a 9-second constant grip hold phase.

EEG, Electromyography, and MRI Acquisition

EEG was recorded from 63 cephalic active surface electrodes referenced to a nose-tip or Cz electrode during recording (BrainAmp MR Plus/actiCHamp amplifier; Brain Products, Gilching, Germany; interim replacement of recording setup). One electrode was mounted below the left eye for electrooculogram recording. Prior to the EEG recording, electrode positions were registered using an ultrasound registration system (Zebris Medical, Isny, Germany). Electromyogram (EMG) was recorded in 10 patients and 9 control participants from the forearm flexors and extensors using disposable silver–silver chloride electrodes. A 3T Siemens Skyra MRI scanner (Siemens, Erlangen, Germany) was used to acquire high-resolution T1-weighted (3-dimensional [3D] magnetization-prepared, rapid acquisition gradient-echo sequence) and T2-weighted (fluid-attenuated inversion-recovery [FLAIR]) anatomical images.

Data Analysis

Analysis was performed with the FieldTrip package for EEG/MEG data analysis, the MEG & EEG toolbox of Hamburg, and SPM12b (University College London, London, UK) on MATLAB (R2017a; MathWorks, Natick, MA), as well as the FSL (University of Oxford, Oxford, UK) and MRIcon software packages (NeuroImaging Tools and Resources Laboratory, Bethesda, MD).

Clinical Data

The NHP test score for each hand was expressed as peg/s to give a performance value. Then, the values of grip force, NHP performance, and UEFMA of the affected arm were divided by the value of the unaffected arm (maximum score = 66 in the case of UEFMA) to give a proportional value (affected/unaffected hand). This way, interindividual variability of strength and fine motor skill was accounted for, and all clinical scores were distributed from 0 to around 1. Stratification of patients into 3 recovery groups was done using standard hierarchical cluster analysis (MATLAB functions linkage, using minimum variance algorithm...
and Euclidean distance, and cluster) based on the initial and 3 months poststroke motor function, assessed as a composite value by the mean of the relative grip force, UEFMA, and NHP performance values. This resulted in group 1, “minimally affected”; group 2, “good recovery”; and group 3, “bad recovery”.

**EEG Data Analysis**

The continuous EEG and EMG signal was high-pass filtered at 1Hz, downsampled to 125Hz, and segmented into epochs of −4 to 3 seconds around the grip onset, determined as the timepoint at which the slope of the recorded force dynamics started to increase. Only trials in which a force buildup was detected were...
used. For the recovery subgroup-specific analysis, we segmented the EEG around the visual stimulus onset and used all available trials. EEG channels with physical artifacts were interpolated, and samples corresponding to eyeblink artifacts were detected based on the signals’ amplitude of electrodes Fp1 and Fp2 and the electro-oculogram and set to NaN. Next, the EEG data were rereferenced to a common cephalic average. All datasets from patients and controls were carefully visually inspected to ensure the absence of extraneuronal signals that could confound the result. Source space activity was reconstructed using linear constrained minimum variance (LCMV) beamforming as described previously.23 We first computed individual head models (geometrical description of the head), source models (location of sources in the brain volume), and forward models (propagation of source activity at locations to the electrodes). The head models were generated as meshes of the inner skull, outer skull, and scalp, describing the boundaries of different head compartments, using the 3D-source space modeling framework of the SPM12 toolbox and individual MRIs. The source models consisted of a regularly spaced (14mm) 3D grid of 548 cortical locations within the brain volume, constrained to the cortex as defined by the AAL atlas (provided by the FieldTrip package). Forward models were computed as boundary element method volume conduction models27 using the MEG & EEG toolbox of Hamburg.26 At each location, a projection matrix describing signal propagation to the electrodes (the leadfield matrix) was computed. The inverse of the leadfield and the covariance matrix of sensor space bandpass-filtered (1–22Hz) time series were used to calculate the LCMV filter oriented along the maximal signal variance. Time frequency representations were calculated from 1 to 22Hz using Hanning tapers with a time window length of 5/frequency, that is, 600 milliseconds at 3Hz, at

**FIGURE 2:** Movement-preparatory low-frequency oscillations (LFOs) are diminished in acute stroke. (A) Breakdown of screening failures. A total of 3,544 stroke patients (excluding transient ischemic attacks) were screened between June 2012 and September 2017 for study eligibility by applying the exclusion criteria listed in the legend sequentially until ineligibility or eligibility (n = 61) was determined. Intracerebral hemorrhages included subarachnoid hemorrhages. MRs = Modified Rankin Scale. (B) Lesion overlay. A summary overview of lesion locations in all 33 stroke patients is shown, with color indicating frequency of lesions. Right-sided lesions were mirrored to the left. LH = left hemisphere; RH = right hemisphere. (C, D) Time–frequency dynamics averaged at contralateral supplementary motor area, primary motor cortex, and anterior intraparietal sulcus, indicating marked reduction in LFO power in acute stroke patients (C) compared to controls (D) prior to grip onset. Power was normalized by a resting period 2 to 4 seconds before grip onset (task-related power [TR-Pow]). Warm colors indicate movement-related increases in power compared to the resting period. (E) Timeline of LFO (3–5Hz, mean ± standard error) power around movement onset in acute patients (acute pat; solid line) and controls (cont; dashed line); thick lines indicate significant deflection from 0 (2-tailed 1-sample t test, p < 0.05). (F) The grip force was significantly lower in stroke patients compared to healthy controls (t = 16.2, p = 3.3 × 10^-12, 2-tailed 2-sample t test, n = 19 and n = 23). (G) Patients had significantly lower average (rectangles in C, D) LFO power compared to controls (t = −2.6, p = 0.01, 2-tailed 2-sample t test).
80-millisecond steps from −4 to 3 seconds around grip onset or visual cue. The data were baseline corrected by the premovement period (−4 to −2 seconds around timepoint 0). EMG data were band-pass (10–60Hz) and band-stop (50Hz) filtered, demeaned, and rectified.

**MRI Data Analysis**

Lesions were segmented on FLAIR datasets, and individual FLAIR datasets were registered to the standard Montreal Neurological Institute (MNI) brain atlas using the MNI brain template with FSL and MRIcron. Lesion overlap was calculated to create a color-coded overlay map of injured voxels across all patients (see Fig 2B).

**Statistics**

Within-group comparisons were performed using 2-sided paired t tests and across-group comparisons using 2-sided unpaired t tests. Statistical comparisons across multiple levels and regressions were done with linear models (LMEs), either linear mixed effects models (LMEs) if a comparison entailed multiple data points of the same participant with participant as a random effect, or simple LMs. Comparisons with clinical data were done separately for each clinical score (grip strength, NHP performance, UEFMA) as the dependent variable and LFO power as the independent variable. The relevance of LFO re-emergence for motor recovery was tested with the change in motor function as the dependent variable and change in LFO power over time as the independent variable. We tested whether the 2 conditions of the grip task, constant output and constant effort, had significantly different LFO power levels using an LME with condition as the fixed effect. No significant difference was found in both groups; thus, we averaged across conditions. To correct for multiple comparisons in the testing of LFOs across the entire cortical sheet (see Figs 1D, 3D), a cluster-based nonparametric randomization test with a cluster-based test statistic of p < .05 was applied.

**Results**

**Temporospatial Pattern of LFOs in a Hand Grip**

We analyzed time–frequency dynamics at 1 to 10Hz around onset of a whole-hand grip (see Fig 1A) in a group of healthy participants (n = 19), age-matched to the patient cohort. A selection of contralateral supplementary motor area (SMA), primary motor cortex (M1), and anterior intraparietal sulcus (aIPS) motor areas were chosen based on peak of activation by the same grip task in a previous functional MRI experiment. Premovement activity was most strongly modulated at 3 to 5Hz, with a significant amplitude increase about 600 milliseconds prior to the grip onset for a duration of about 600 milliseconds. EMG activity, recorded from the forearm flexors, started about 400 milliseconds prior to the grip onset (see Fig 1). Thus, in human whole hand grip,
LFOs appear in the movement preparatory period. We projected the LFO power during this time–frequency window (3–5Hz, −600 to 0 milliseconds) onto the cortical sheet and found significant power increases in a widespread cortical cluster, predominantly at the contralateral sensorimotor cortices, including premotor, SMA, and parietal areas (see Fig 1). All the a priori defined motor areas (aIPS, M1, SMA) except PMv were part of this cluster. Further analysis of movement-related LFO dynamics were focused on those areas (aIPS, M1, SMA). In the frontal lobe, an activation peak occurred in the medial frontal gyrus (Table 1). Movement-preparatory LFOs time-locked to the visual cue showed a similar temporospatial pattern. There was no significant difference in LFO power between the different motor areas ($F_{1, 55} = 0.04, p = 0.86$, LME, n = 19). Two conditions of varying grip force, 5 kg and 20% maximum voluntary contraction, showed no significant difference in LFO power ($F_{1, 35} = 0.2, p = 0.65$, LME, n = 19), as shown previously for task-related alpha and beta rhythm modulation. Inter-individual variance in LFO power did not significantly covary with differences in grip force ($F_{1, 17} = 0.13, p = 0.72$, LM, n = 19) or fine motor skills (NHP value, $F_{1, 16} = 0.58, p = 0.58$, LM, n = 18).

The temporospatial dynamics, visualized in the Supplementary Video, demonstrate a posterior to anterior spreading of LFO power preceding the grip onset (see Fig 1F).

**Movement-Preparatory LFOs Are Diminished after Acute Motor Stroke**

We screened a total of 3,544 patients with acute stroke and symptoms lasting >24 hours. Sixty-one patients with an acute (3–5 days) first ever ischemic stroke causing a motor deficit involving hand function were eligible (see Fig 2A). Longitudinal task-related EEG measurements (see Fig 1A) at the acute (3–5 days), early subacute (1 month), and late subacute (3 months) stage without loss to follow-up were available from 33 patients. Patients had predominantly subcortical (n = 21) strokes followed by mixed cortical and subcortical (n = 11) and 1 purely cortical stroke (lesion volume = 17.5 ± 25 ml; see Supplementary Table, Fig 2B). Of those, we selected patients who were able to generate
enough force to perform the grip task even in the acute stage (n = 23, age = 64.1 ± 2.3 years mean ± SE, 7 females, 2 left-handed) for a comparison of LFO power with the healthy participants. The patients had impaired motor function, quantified with the grip force (patients 21 ± 2kg vs controls 34 ± 2.1kg; see Fig 2F), upper extremity active movement range and synergies (UEFMA = 56.3 ± 2.3, highest score = 66), and fine motor skills (NHP, patients 0.44 ± 0.07 vs controls 1.1 ± 0.03; see Supplementary Table). The average LFOs in the specified time–frequency window (−600 to 0 milliseconds around grip onset, 3–5Hz) in acute stroke patients were significantly reduced to a level of 38% of the power in healthy controls (t = −2.6, p = 0.01), indicating that movement-related LFOs do not result from activity phase-locked to the grip onset. There was no association between cortical lesion and pure subcortical location of the lesion and the LFO power (F1, 20 = 0.28, p = 0.6) nor the lesion volume (F1, 20 = 1.20, p = 0.28). The group difference between LFO power was not related to the difference in grip force between groups (F1, 38 = 0.28, p = 0.6, LM interaction group × grip force, n = 19 and n = 23).

Movement-Preparatory LFOs Remerge with Time after Stroke

With the passage of time after stroke, movement-preparatory LFOs gradually became stronger and reached an amplitude comparable to that of the control participants by 3 months after stroke (F1, 67 = 17.1, p = 9.8 × 10−5, LME, n = 23, see Fig 3). Again, this result was confirmed after subtracting the mean movement

### TABLE 1. Regional Peaks in Movement-Related LFO Activity in Control Participants

| Brain Area           | Motor Cortical Areas          | t   | LFO Power | MNI Coordinates, x, y, z |
|----------------------|-------------------------------|-----|-----------|--------------------------|
| **LH**               |                               |     |           |                          |
| Medial frontal gyrus |                               | −4.59 | 0.32     | −34, 0, 53               |
| Paracentral lobule   | MPMC, SMC, M1                 | −5.24 | 0.52     | −6, −28, 53              |
| Inferior parietal gyrus |                           | −4.62 | 0.45     | −34, −42, 39             |
| Superior temporal gyrus |                            | −2.19 | 0.29     | −62, −28, 11             |
| Inferior temporal gyrus |                            | −3.30 | 0.34     | −62, −56, −16            |
| Middle temporal gyrus |                               | −3.70 | 0.32     | −62, −56, 11             |
| Lingual gyrus        |                               | −3.98 | 0.25     | −34, −84, −16            |
| Middle occipital gyrus |                          | −3.11 | 0.28     | −34, −84, 11             |
| **RH**               |                               |     |           |                          |
| SMA                  | MPMC, pre-SMA                 | −3.56 | 0.33     | 7, 27, 53                |
| Precentral cortex    | LPMC, PMd, SMC, M1, S1        | −3.83 | 0.23     | 35, −14, 39              |
| Superior temporal gyrus |                           | −2.18 | 0.2      | 63, −14, 11              |
| Inferior temporal gyrus |                         | −3.63 | 0.2      | 63, −28, −16             |
| Inferior temporal gyrus |                         | −3.19 | 0.33     | 49, −70, −2              |
| Calcarine fissure    |                               | −2.87 | 0.29     | 21, −56, 11              |
| Middle occipital gyrus |                          | −3.49 | 0.33     | 35, −84, 11              |

T-values were obtained from voxelwise 1-sample t test (n = 19), corrected for multiple comparisons using permutation-based cluster thresholding. All coordinates are within the same cluster.

LFO = low-frequency oscillation; LH = left hemisphere; LPMC = lateral premotor cortex; M1 = primary motor cortex; MNI = Montreal Neurological Institute; MPMC = mesial premotor cortex; PMd = dorsal premotor; RH = right hemisphere; S1 = somatosensory cortex; SMA = supplementary motor area; SMC = sensorimotor cortex.
TABLE 2. Peak Coordinates for Time-Dependent Changes in Movement-Related LFO Activity from the Acute to the Early and Late Subacute Phase Poststroke

| Area                  | Z  | Δ Power | MNI Coordinates, x, y, z |
|-----------------------|----|---------|-------------------------|
| LH                    |    |         |                         |
| Postcentral cortex    | 4.12 | 0.28   | −34, −28, 53            |
| Inferior parietal cortex | 3.89 | 0.26   | −48, −56, 53            |
| Cuneus                | 3.38 | 0.22   | −6, −84, 25             |
| Middle occipital gyrus | 2.88 | 0.19   | −34, −70, 11            |
| Inferior occipital gyrus | 2.11 | 0.17   | −48, −70, −16           |
| Superior occipital gyrus | 4.07 | 0.36   | 21, −84, 25             |
| RH                    |    |         |                         |
| Occipital cortex inferior | 19.23 | 0.35 | −84, −2                |

$\Delta$ Power = LFO power late subacute − LFO power acute.

LFO = low-frequency oscillation; LH = left hemisphere; MNI = Montreal Neurological Institute; RH = right hemisphere.

F values of factor Time from voxelwise linear mixed effects model (n = 23), corrected for multiple comparisons using permutation-based cluster thresholding. LFO = low-frequency oscillation; LH = left hemisphere; MNI = Montreal Neurological Institute; RH = right hemisphere.

event-related potential from each trial before spectral analysis ($F_{1,67} = 11.4, p = 0.001$), indicating that movement-related LFOs do not result from activity phase-locked to the grip onset. The 2 conditions of varying grip force showed no significant difference in LFO power ($F_{1,130} = 0.71, p = 0.4$, LME, n = 23) or interaction of condition with time after stroke ($F_{1,128} = 0.48, p = 0.49$, LME, n = 23). The pattern of the re-emerged LFO dynamics showed a similar spectral (3–5Hz) and temporal pattern (beginning around 600 milliseconds before grip onset) to that of the LFO dynamics in healthy participants. The topography of time-dependent increases in LFO power revealed primarily a contralateral sensorimotor cluster of frontal and parietal areas, also spanning temporal regions (see Fig 3D, Table 2).

Movement-Related LFO Power Is Related to Motor Function and Motor Recovery

Patients showed a significant increase of hand motor function from the acute stage to the late subacute stage, indicated by the grip force ($F_{1,67} = 35.7, p = 9.4 \times 10^{-8}$, LME, n = 23), UEFMA ($F_{1,67} = 20.2, p = 2.88 \times 10^{-5}$), and NHP value ($F_{1,67} = 39.5, p = 2.8 \times 10^{-8}$). Movement-related LFOs positively covaried with various qualities of motor function including force, movement synergies, and fine motor control (grip force: model estimate 0.51, $F_{1,67} = 15.1, p = 2 \times 10^{-4}$, LME, n = 23; UEFMA: model estimate 0.73, $F_{1,67} = 10.7, p = 0.002$; NHP performance: model estimate 0.39, $F_{1,67} = 17.8, p = 7.6 \times 10^{-5}$). Given possible changes in the motor function of the unaffected hand after stroke, we confirmed this result with a correlation using non-normalized grip force and NHP values at all 3 timepoints (grip force: $F_{1,67} = 33.4, p = 2 \times 10^{-7}$, LME, n = 23; NHP performance: $F_{1,67} = 10.7, p = 1 \times 10^{-3}$). We tested whether the re-emergence of LFOs in the contralateral sensorimotor cortex is related to the recovery of hand motor function by correlating the change in grip force from the acute to the early and late subacute stage with the change in LFO power in the same period. Patients with a stronger recovery of grip force also display a stronger re-emergence of LFOs (grip force: model estimate 0.42, $F_{1,44} = 6.5, p = 0.02$, LME, n = 23; UEFMA: model estimate 0.50, $F_{1,44} = 4.6, p = 0.04$, see Fig 4C; NHP performance: model estimate 0.38, $F_{1,44} = 5.06, p = 0.03$). Similarly, using non-normalized grip force confirmed this result ($F_{1,44} = 22.4, p = 2 \times 10^{-5}$, LME, n = 23), whereas non-normalized NHP values did not significantly covary with changes in LFO power.

LFO power was also compared to movement parameters closely related to the kinematics during the grip task. We assessed grip stability as the coefficient of variation of grip force buildup (0–2 seconds after movement onset) and the time to grip onset after the visual cue. Both parameters covaried with LFO power (grip force stability: model estimate −0.33, $F_{1,66} = 20.6, p = 2.4 \times 10^{-5}$, n = 23; time to grip onset: model estimate −0.31, $F_{1,66} = 15.9, p = 1.7 \times 10^{-4}$, n = 23). The increase in grip force stability over time covaried with increase in movement-related LFO power (model estimate −0.39, $F_{1,42} = 5.7, p = 0.02$, LME, n = 23).

A small increase in motor function from the acute stage to the late subacute stage could occur either in patients who are only minimally affected at the acute stage, or in patients who are severely affected and do not recover. To study LFO patterns including severely affected patients, we included all patients (n = 33; previous analyses were restricted to patients with measurable force production) and quantified LFO power in a window after the visual “go” cue (0–600 milliseconds). To identify whether a particular recovery pattern is associated with re-emergence of movement-related LFOs in the time
poststroke, we performed a cluster analysis on the initial and 3 months poststroke motor function (composite value by the mean of the relative grip force, UEFMA, and NHP performance values, see Subjects and Methods section). The algorithm stratified patients into 3 groups of variable recovery: “minimally affected” (n = 10), “good recovery” (n = 18), and “bad recovery” (n = 5; see Fig 4D). Consistent increases in LFO power from the acute to the late subacute stage were only present in the “good recovery” (see Fig 4E) group, whereas the group of patients with a little initial deficit or bad recovery did not show a consistent re-emergence of LFOs. It appears as if the re-emergence of LFO power during the movement preparatory period may be a marker of the recovery process. The validity of this analysis is limited by the small sample size, especially in the nonrecovering group (n = 5).

Specificity of Power Re-emergence to LFOs
Known pathophysiology in stroke-lesioned brains is a reduction of the modulation of the sensorimotor beta rhythm in chronic stroke patients compared to healthy subjects.23,29,30 Also, current experimental approaches of noninvasive brain-computer interfaces for upper limb rehabilitation mostly exploit the sensorimotor alpha and beta rhythms.31,32 Thus, we tested whether the described diminishment of movement-related LFOs poststroke and re-emergence are specific for LFOs, or whether similar patterns occur in typically studied sensorimotor rhythms in the alpha and beta range (Fig 5). We first analyzed the temporal pattern of alpha (8–13Hz) and beta (15–22Hz) modulation around grip onset in the healthy controls. Unlike movement-related LFOs, the alpha and beta rhythms showed a sustained decrease in amplitude throughout grip execution, which corresponds to the well-known phenomenon of event-related desynchronization.33 aIPS showed the strongest movement-related alpha and beta decrease (averaged over time–frequency window indicated by rectangle in Fig 5), followed by M1 (SMA, M1, aIPS; beta: $F_{1, 55} = 18.8, p = 6.4 \times 10^{-3}, \text{LME factor region, } n = 19$; alpha: $F_{1, 55} = 45.0, p = 1 \times 10^{-8}, \text{LME factor region, } n = 19$). At aIPS, the beta rhythm modulation in the acute stage poststroke was significantly less compared to healthy controls ($t = −2.8, p = 0.007$, 2-tailed 2-sample $t$ test, n = 23 and n = 19), and, consistent with previous work, also in the late subacute stage ($t = −3, p = 0.005$, 2-tailed 2-sample $t$ test, n = 23 and n = 19). At none of the timepoints did movement-related alpha power significantly differ between patients and controls. None of the regions showed consistent changes in the modulation of alpha or beta rhythm amplitude over time ($p > 0.05$, LME, n = 23). Despite the lack of time-dependent changes of alpha and beta rhythm modulation, patients with a stronger recovery of grip force displayed a stronger movement-related modulation of the beta rhythm (model estimate $–0.61, F_{1, 44} = 16.4, p = 0.0002, \text{LME, } n = 23$). The strength of the beta rhythm amplitude modulation also correlated with the UEFMA (model estimate $–1.02, F_{1, 47} = 13.6, p = 0.0005$), and a stronger increase in UEFMA over time went along with a stronger modulation of beta power amplitude (model estimate $–0.81, F_{1, 44} = 16.5, p = 0.0002, \text{LME, } n = 23$). There were no significant correlations between fine motor skills and recovery thereof and alpha or beta rhythm modulation (Fig 5).

Discussion
We show that short bouts of LFO activity appear at motor cortices before movement in the healthy human brain. Longitudinal movement-related recordings in patients show that cortical circuit dysfunction after stroke is marked by a lack of coordinated LFO activity in the human brain in proportion to the motor deficit. A normalization of this cortical dysfunction tracks the recovery of the motor deficit.

Physiologic Role of Movement-Related LFOs
Previous studies using invasive recordings suggested that motor cortical movement-related LFOs control movement type, 3D movement trajectories, and velocity.17,18 Distinct LFO components are related to different submovements, indicating that they may be of relevance for the precise temporal coordination of movements and sequencing of motor actions.34 A mechanistic role in cortical LFOs for precise motor control is supported by animal stroke models, including neuromodulation.16 Prior invasive recordings in animals focused on a priori selected cortical sites, and human data, better allowing whole-brain coverage, are sparse,16,19 with the temporospatial pattern of LFO dynamics during movement preparation being unknown. We here characterized the cortex-wide distribution of movement-related LFOs in healthy humans performing a visually guided whole hand grip task. The data revealed that LFO activity increases well preceding motor onset and in a frequency range of 3 to 5Hz at predominantly contralateral frontoparietal motor regions. The similarity of the temporospatial pattern of LFO dynamics in humans described here to focal animal recordings suggests that LFOs serve a similar function in setting a preparatory state in humans. LFO activity during cognitive motor tasks reflects a differential involvement of the ventral visual stream, suggesting that LFOs may contribute to sensorimotor integration along relevant sensorimotor network locations.19 We found LFOs to propagate in a posterior to anterior direction prior to movement onset, in an extended cluster including occipital and temporal areas, with a peak of activity at
parietal and frontal motor areas (see Figs 1F, 2, Supplementary Video). An intrinsic (top-down) as opposed to extrinsic (bottom-up, feedback) cortical origin of low-frequency cortical dynamics during submovements is supported by their similarity to cyclic activity during sleep and pharmacologic sedation, as well their emergence well before movements (see Fig 1), when movement-accompanying sensory input is yet to come. Also, previous studies have provided evidence that motor cortical LFOs represent an "induced" oscillation and do not result from activity phase-locked to the movement, like slow motor-related potentials. Time-locked, "evoked," transient signal fluctuations can have an oscillatory waveform picked up by spectral analysis. Presumably, "evoked" and "induced" brain responses also share some common generators, and it is worth looking at both kinds of signals to understand stroke pathophysiology.

**Diminishment of Movement-Related LFOs in Stroke Pathophysiology**

We show in longitudinal recordings in human patients that movement-related LFOs in the motor cortex are significantly disrupted by an acute stroke (see Fig 2). Several ischemia- and injury-related changes in cortical physiology could contribute to a diminished level of LFOs. Aberrant mesocircuit network properties immediately following stroke in the perilesional cortex lead to an altered balance between inhibitory GABAergic and excitatory glutamatergic signaling. The onset of restorative processes like neurogenesis, gliogenesis, and axonal sprouting also affect synaptic activity, likely impacting on population synchronization, which is a prerequisite for measurable macroscale current dipoles. Impairment after stroke results from local damage as well as network disruption due to diaschisis from connected regions leading to reduced synaptic input. Network disruption may impair the temporal coordination between LFO-relevant neural ensembles, leading to a reduced populational activity. We found that movement-related LFOs in the stroke-lesioned hemisphere gradually increased with time after stroke, presumably as a result of biological repair mechanisms involving plasticity. Lesion-induced plasticity in the human brain has been demonstrated in the form of a reorganization of task-specific networks, for example, the parietofrontal dorsolateral and dorsomedial network. To date, integrity of the corticospinal tract, a lateralized activation pattern in motor cortical regions, M1–M1 interhemispheric connectivity, and the strength of the beta rebound, among others, are known factors determining the degree of recovery of motor function in human stroke patients. Neural oscillations offer a functional perspective on poststroke plasticity, as they are linked to excitatory and inhibitory tone in cortical microcircuits, receptor functioning at the microscale level, and global brain network dynamics at the macroscopic level. In human stroke research, commonly studied rhythms are the sensorimotor alpha (8–13Hz) and beta (15–22Hz) rhythms. The strength of the beta rhythm rebound after sensory stimulation and passive movements of the affected hand is related to motor impairment and recovery therefrom. During active movements of the affected hand, a smaller beta desynchronization in contralateral M1 has consistently been found in chronic stroke.

![FIGURE 5: Sensorimotor alpha and beta rhythms after stroke and in healthy subjects. (A, B) Time–frequency dynamics at anterior intraparietal sulcus at the acute (3–5 days), subacute (1 month), and late subacute (3 months) stage poststroke (A) as well as in controls (B), showing a less pronounced modulation of alpha and beta rhythms in stroke patients. Power was normalized by a resting period 2 to 4 seconds before grip onset (task-related power [TR-Pow]). Cold colors indicate movement-related decreases in power compared to the resting period. (C) Average beta power (15–22Hz, upper rectangles in A, B) did not significantly change over time. The stroke patients showed significantly less beta rhythm power decrease than the controls (cont) at the acute ($t = -2.8$, **$p = 0.007$, 2-tailed 2-sample t test, n = 23 and n = 19), early subacute ($t = -2.4$, *$p = 0.02$), and late subacute ($t = -3$, **$p = 0.005$) stage.](image-url)
patients that is related to the degree of impairment. Our longitudinal recordings demonstrate that this reduced level of movement-related beta desynchronization is already present at the acute stage. This indicates that reduced beta modulation is not the result of poststroke plasticity but likely contingent on altered homeostasis between excitatory and inhibitory circuits already early after stroke. However, we found a consistent pattern of time-dependent changes after stroke only in the LFO dynamics, underlining their close link to stroke-specific pathology. Given their appearance prior to movement onset, LFO dynamics are particularly interesting as targets for interventional therapy. Interestingly, apart from predominantly ipsilesional, also contralesional occipital regions showed time-dependent increases in LFO power. The occipital areas spatially correspond to the parieto-occipital complex, which is a pathway for early visuomotor integration along the dorsal stream, as well as the lateral occipital cortex, representing motor action at higher cognitive levels. Given the posterior–anterior propagation of LFOs between visual cue and movement onset, this may indicate a local signal upregulation due to insufficient conduction or missing feedback from motor areas.

**Movement-Related LFOs May Support Functional Recovery**

The re-emergence of LFOs paralleled motor recovery, with a stronger increase in patients who showed a better recovery and no relevant increases in LFOs in nonrecovering patients (see Fig 4). Given previous neurostimulation experiments in rodents, a mechanistic link between the increase in LFOs and improvement of motor function is conceivable also in humans. Recovery of motor function went along with an increase in LFO power, with changes in UEFMA (measuring upper extremity active movement range and synergies) being most closely linked to LFO re-emergence (model estimate 0.50), followed by grip force (model estimate 0.42), stability of grip force (model estimate −0.39), and NHP (fine motor skills, model estimate 0.38). Seemingly, a variety of movement aspects are linked to LFO re-emergence, which would be in line with the documented role of LFOs in grip preparation and differentiation and ventral stream processing. However, recovery of different movement aspects is highly correlated; thus, it is possible that LFOs re-emergence is more movement quality specific and some correlations with recovery detected here are spurious.

In human stroke survivors who fail to show spontaneous recovery, on-demand neurostimulation in the form of short bouts shortly before a movement could induce pathologically diminished LFOs, thereby compensating for insufficient endogenous generation. On-demand cortical neurostimulation was shown to improve skillful reaching and grasping after stroke in rodents. The stimulation reinstalled transient cortical movement-related LFOs that were diminished in stroke-lesioned rats. This approach is conceptually different from previous attempts to support neurorehabilitation after stroke, which primarily act on enhancing neuroplasticity and augmenting functional reorganization. Its mechanism of action is to supply on-demand, task-related signals to areas that are pathophysiologically absent and thereby normalizing neural coding downstream of the stroke lesion for proper task execution and represents a mechanistic form of neuroprosthetic therapy. Mechanistic stimulation approaches have been successfully implemented to reinstate ambulation in spinal cord injury in primates, but so far do not exist for human stroke survivors. By design, neuroprosthetic approaches warrant a close link between pathophysiology and the stimulation effect, but suitable stimulation targets in stroke patients were so far largely unknown. The here presented identification of LFOs as a recovery-related brain signal that can easily be recorded in humans well before movement onset and even with a limited electrode montage, together with the promising target engagement via neurostimulation in a rodent model of stroke, suggests that it might be worthwhile to address the restitution of LFOs as a mechanistic target for brain stimulation in human stroke survivors.

**Limitations**

Several limitations should be acknowledged, and cautions taken accordingly. First, although the sample size in the present longitudinal poststroke task-related electrophysiological recordings exceeds previous studies, it is too small for well-powered statistical analyses on subgroups. Second, although a causal role of LFOs on motor control and planning was brought forward by recent stimulation experiments in rodents, our data provide merely a correlative relationship between LFO power and motor function. Third, source activity between close targets is hard to unambiguously separate. Although advanced spatial reconstruction methods can separate activity from aIPS and M1, and this study benefits from previously identified individual motor coordinates in an overlapping patient and control population using the same motor task, we cannot claim spatial accuracy at those targets.

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Author Contributions
C.G., M.B.: conception and design of the study; M.B., L.K., R.S., B.C., J.F.: data acquisition and analysis; M.B.: drafting the text and preparing the figures; all authors: editing and approving the text.

Potential Conflicts of Interest
Nothing to report.

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