Study protocol BNP-2020-09

Personalized neurorehabilitative precision medicine – from data to therapies

(Acronym: MWKNeuroReha)

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Summary:

Stroke is the most common neurological disease leaving one third dead and one third with permanent impairment despite best medical treatment. The aim of the present study is to investigate why patients differ in how they benefit from neurorehabilitation by collecting clinical, electrophysiological, imaging and laboratory data in the acute phase of stroke as well as later on during rehabilitation and after 90 days. Following a closed-loop approach the data is analyzed by a machine learning algorithm to create a personalized neurorehabilitation strategy.

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1. Study title

Personalized neurorehabilitative precision medicine – from data to therapies

2. Study responsibilities

2.1 Sponsor

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2.4 Project partners

In charge:

- Hertie-Institut für klinische Hirnforschung, Universität Tübingen, Ottfried-Müller-Str. 25, 72076 Tübingen

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- Interfakultäres Institut für Biomedizinische Informatik (IBMI), Universität Tübingen, Sand 14, 72076 Tübingen
- Exzellenzcluster Maschinelles Lernen, Universität Tübingen, Maria-von-Linden-Str. 6, 72076 Tübingen
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- SRH-Kliniken, Standorte Bad Wimpfen (Bei der alten Saline 2, 74206 Bad Wimpfen), Karlsbad-Langensteinbach (Guttmannstr. 1, 76307 Karlsbad), Bad Dobel (Neuenbürger Str. 49, 75335 Dobel) und Waldbronn (Gisela-und-Hans-Ruland-Str. 1, 76337 Waldbronn)
- Zentrum für ambulante Rehabilitation (ZAR), Hoppe-Seyler-Str. 6, 72076 Tübingen, im Gesundheitszentrum Gebäude 480
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- Kliniken Calw, Edouard-Conz-Straße 6, 75365 Calw
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- Kreiskliniken Reutlingen GmbH, Steinenbergstraße 31, 72764 Reutlingen
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There will be processing contracts (Auftragsverarbeiter-Vertrag) in accordance with § 26 of the general data protection regulation (Datenschutzgrundverordnung) with each cooperative partner and subcontractor.

2.5 Institutional Review Board/Ethics Review Committee

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3. Signatures

3.1 Principal investigator (PI) and Leiter der klinischen Prüfung (LKP)

I agree to conduct and document this clinical study in accordance with the design outlines in this protocol.

Typed name:	Signature:	Date:
Prof. Ulf Ziemann	_____	_____

3.2 Investigators

I agree to conduct and document this clinical study in accordance with the design outlines in this protocol.

Typed name:	Signature:	Date:
Dr. med. David Baur	_____	_____
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Dr. med. Brigitte Zrenner	_____	_____
PD Dr. med. Felix Fluri	_____	_____

4. Funding

This study is funded by “Forum Gesundheitsstandort Baden-Württemberg” of the “Ministerium für Wissenschaft, Forschung und Kunst Baden-Württemberg“ (540.000,0 € to U. Z.).

5. List of abbreviations

ARAT	Action Research Arm Test
ASTRAL score	Acute Stroke Registry and Analysis of Lausanne score
BDI	Beck's Depression Inventory
BI	Barthel Index
CST	Corticospinal tract
CT	Computed tomography
DWI	diffusion weighted imaging
EEG	Electroencephalography
EMG	Electromyography
EOG	Electrooculography
FLAIR	fluid attenuated inversion recovery
FMA	Fugl-Meyer-Assessment
fMRI	Functional MRI
CRP	C-reactive protein
K	potassium
M1	Primary motor cortex
MEP MEP+ MEP-	Motor evoked potential MEP positive MEP negative
MP-RAGE	Magnetic Prepared-Rapid Gradient Echo
MRI	Magnet resonance imaging
mRS	Modified ranking scale
Na	sodium
NIHSS	National Institute of Health Stroke Scale
NT-proBNP	N-terminal proBrain natriuretic peptide
RMT	resting motor threshold
rt-PA	recombinant tissue plasminogen activator
SAFE	Shoulder abduction finger extension
SAN	Storage area network
sMRI	Structural MRI
SS-QOL	Stroke specific Quality of life scale
SU	Stroke Unit
TEP	TMS evoked potential
TMS	Transcranial magnetic stimulation
UE	Upper extremity
UKT	Universitätsklinikum Tübingen

6. Introduction and background

Stroke is the most common neurological disease leaving one third dead and one third with permanent impairment despite best medical treatment (Makris et al. 2018). In ischemic stroke a vessel is occluded resulting in a shortage of oxygen and glucose which leads ultimately to cell death. In the first hours after symptom onset the extent of damage can be limited by administrating recombinant tissue plasminogen activator (rt-PA) to resolve the blood clot or reopening the vessel via catheter-directed thrombolysis. However, once the critical time limit is exceeded, there is no underlying treatment option left and brain damage is permanent. In this stage, therapy aims to prevent additional damage (e. g. by swelling) and reoccurrence of stroke. In case of hemorrhagic stroke treatment is even more limited, being restricted to pure symptomatic care. Even more important is neurorehabilitation to reinstate lost functions which is already initiated in the Stroke Unit (SU) and continued and intensified in rehabilitation facilities.

Even though patients can suffer from a multitude of strokes (e. g. lacunary or territorial infarction) in different locations (e. g. cortex, corona radiata or brain stem) ranging from very mild (e. g. light paresis of an arm) to very severe (e. g. hemiplegia together with reduced consciousness and aphasia) caused by multitude of reasons (e. g. atrial fibrillation or microangiopathy) while suffering from different preconditions (e. g. arterial hypertension or dementia), usually for one symptom always the same rehabilitation procedure is applied (albeit being adapted to the patient's fitness and abilities). Given this heterogenous picture it is probably not surprising that some patients benefit very well from rehabilitation treatment while some do not at all.

The present study investigates which factors contribute to how patients benefit from neurorehabilitation by collecting clinical, electrophysiological, imaging and laboratory data in the acute phase of stroke as well as later during rehabilitation and after 90 days. Following a closed-loop approach the data is analyzed by a machine learning algorithm to create a personalized neurorehabilitation strategy.

The study will be restricted to patients with impairment of the upper extremity (UE) since it is a very common and also disabling deficit after stroke which can easily be evaluated by clinical assessment scores (e. g. Fugl-Meyer-Assessment (FMA)).

7. Scientific rationale

Stroke is the result of a mismatch of energy supply and consumption. Discontinuity of blood flow leads to energy failure due to missing glucose and adenosine triphosphate (ATP) which in turn leads to failure of the sodium-potassium-ATPase (Na-K-ATPase) resulting in uncontrolled depolarization and consecutive toxic edema and release of glutamate inducing oxidative stress with microvascular injury and breakdown of the blood brain barrier, inflammation and cell death (Makris et al. 2018).

Stroke leads to disruption of functional connectivity affecting also remote areas, reduced interhemispheric connectivity (assessed by resting-state functional magnetic resonance imaging (fMRI)) (Puig et al. 2018; Thiel und Vahdat 2015; Park et al. 2011) and disturbed balance of inhibition and excitation: Task-related fMRI shows increased activity in the contralesional primary motor cortex

(M1) inhibiting the ipsilesional M1 when moving the paretic hand while the inhibitory influence of the contralesional supplementary motor area is reduced (Grefkes et al. 2008; Rehme et al. 2011). Impaired connectivity in stroke can also be shown using electroencephalography (EEG). For example, transcranial magnetic stimulation (TMS) evoked potentials (TEPs) of the ipsilesional cortex lead to slower, simplified responses with high amplitudes correlating with the severity of motor impairment and reflecting disruption of cortico-cortical and cortico-subcortical networks (Tscherpel et al. 2020), while abnormal delta activity mirrors deafferentation and correlates with regional cerebral blood flow (Sheorajpanday et al. 2011; Finnigan und van Putten 2013).

In the first month after stroke the largest amount of recovery happens reaching a plateau after three months (Zeiler 2019). It varies depending on volume and localization of stroke lesion, clinical severity of stroke and integrity of the corticospinal tract (CST) (Kasner 2006, Kim und Winstein 2017, Stinear et al. 2017).

Motor evoked potentials (MEPs) can be used to measure the integrity of the CST. The presence of MEPs is highly predictive for good motor outcome. As expected, the absence of MEPs is a predictor for poor outcome, however, this association is less reliable, since some patient achieve a good motor outcome besides being MEP negative (MEP-) (van Kuijk et al. 2009). Indeed, by eliciting MEPs with a paired-pulse protocol, Leão et al. (2020) could re-classify 65 % of MEP- patients as MEP positive (MEP+).

EEG can be used to calculate the (pairwise-derived) brain symmetry index ((pd)BSI) and the (delta+theta)/(alpha+beta) power ratio (DTABR). The BSI (or pdBSI if the data is assessed from homologue channels from both hemispheres) describes the left-right power (a)symmetry by quantifying the difference in mean spectral power per hemisphere across 1-25 Hz (Finnigan und van Putten 2013; Sheorajpanday et al. 2011). As the term DTABR already implicates, slow (delta and theta) and fast (alpha and beta) brain oscillations are put in relation to each other. The DTABR und the pdBSI predict impairment as rated by the modified Rankin Scale (mRS) after 6 months (Finnigan und van Putten 2013; Sheorajpanday et al. 2011).

The perturbational complexity index (PCI) can be derived from TEPs. It is a measure of brain complexity reflecting interaction among cortical areas (integration) and distinct responses of those interacting areas (differentiation), discriminating reliably between conscious and unconscious patients (Casali et al. 2013). In patients with unresponsive wakeful syndrome the brain acts like being in non-rapid eye movement (REM)-sleep, where thalamocortical circuits are structurally and functionally intact, but unable to engage in long-range complex responses because of so called OFF periods during which firing of neurons is suppressed due to hyperpolarization (Rosanova et al. 2018). A similar phenomenon is observed locally in patients with subcortical strokes (Fanciullacci et al. 2017).

As explained above inflammation is part of the cascade triggered by stroke. This might be reflected by increased C-reactive protein (CRP) which is associated with poor long-term outcome (VanGilder et al. 2014). Other blood biomarkers are for example d-dimers, N-terminal proBrain natriuretic peptide (NT-proBNP) and troponin (He et al. 2018; Hatanu et al. 2018; Maruyama et al. 2017).

Despite years of research and clinical practice, up to date it is neither possible to predict motor outcome after stroke reliably, nor to recommend the best course of rehabilitation treatment (Zeiler 2019), although there were several attempts: For example, Stinear et al. (2017) created an algorithm (Predict Recovery Potential 2 (PREP 2)) which included testing of shoulder abduction and finger extension, age as well as presence or absence of MEPs that at least determined outcome of UE correctly for 75 % of their cases. However, obviously 25 % of their patients were still incorrectly classified. The present study aims not only to close this knowledge gap but also strives to optimize

rehabilitation treatment to improve stroke outcome by collecting data from acute stroke patients on the SU as well as later on in the rehabilitation facility and analyze them with a machine learning algorithm.

Machine learning is a method in which a computer algorithm learns for instance to identify something on a picture or make a correct diagnosis (here: to predict motor outcome in stroke) from a given data set by using already existing correct data sets as example. It is especially superior in identifying patterns humans might miss (Saber et al. 2019). Indeed, Heo et al. (2019) showed that a machine learning algorithm was better in predicting stroke outcome than the Acute Stroke Registry and Analysis of Lausanne (ASTRAL) score (which is a an score for predicting stroke outcome with good discriminatory power for good and poor outcome (Drozdowska et al. 2019)). By adding the results of the follow-up assessments, the machine learning algorithm can correct and finetune itself, which is in accordance with a closed-loop approach.

For each patient with acute stroke affecting the UE, data is collected consisting of clinical tests to describe the impairment and the severity of stroke, structural and functional magnet resonance imaging (sMRI and fMRI, respectively), MEPs, EEG, TEPs and a laboratory workup. After discharge, rehabilitation treatment is monitored and added to the data set of each patient. On admission to one of the cooperating neurorehabilitation hospitals and at intervals of 14 days, impairment and disability are tested again to quantify longitudinally stroke recovery. 90 days after stroke impairment of the UE is measured (primary endpoint), furthermore range of activity of the UE, dependency in daily life and quality of life is assessed (secondary endpoints). Moreover, during the inpatient period in the neurorehabilitation hospitals, the amount and types of neurorehabilitative treatments will be recorded.

8. Summary of study

8.1 Study design

Multicenter observational study.

8.2 Number of subjects

We intend to include 500 acute stroke patients during the funding period.

8.3 Study duration

The study is planned to span a duration of 2 years between June 1st, 2020 and May 30th, 2022. The study duration of each subject is 90 days.

8.4 Measurement procedures

Clinical tests: Each subject will be assessed using the following tests:

National Institute of Health Stroke Scale (NIHSS): The NIHSS is part of the usual highly standardized stroke workup. It consists of 15 items which can be scored with 0 to 4 points maximum. It is used to measure stroke severity as well as impairment and to detect improvement or deterioration of the patient. A high score corresponds to a severe stroke (Brott et al. 1989).

FMA for UE and sensory system: The FMA for the UE and the sensory system describes the sensory-motor impairment of the arm after stroke. It consists of 66 items for the motor function of the UE and 24 items for the sensory function scored from 0 to 2. A high score corresponds to high function (Gladstone et al. 2002). It is not part of the usual stroke workup. The change of the FMA for UE after 90 days compared to the first score obtained on the stroke unit during the acute phase of the stroke event will serve as the primary endpoint of this study.

Shoulder abduction finger extension (SAFE) score: To calculate the SAFE score shoulder abduction and finger extension is measured using the classification of the British Medical Research Council (MRC). The MRC scale scores muscle strength from 0 (no movement) to 5 (normal power) (Compston 2010). The scores are added up producing a value from 0 to 10. A score of 5 or more predicts a good or excellent outcome after stroke affecting the UE (Stinear et al. 2017). It is not part of the usual stroke workup.

Grip strength: The grip strength can be quantified using a dynamometer. The best out of three trials counts. It is not part of the usual stroke workup.

Bells test: The Bells test assesses neglect by requesting the subjects to cross all the bells (n = 35) which are mixed with distractors. Missing 5 bells counts as evidence for neglect (Ferber und Karnath 2002). It is not part of the usual stroke workup.

Aphasie-Schnelltest (AST): The AST is a short test for patients with acute aphasia scored from 0 to 31 and inspecting comprehension, talking, reading, and writing. A low score reflects severe aphasia. (Kroker 2006). It is not part of the usual stroke workup.

mRS: The mRS is a widely used test to determine impairment and dependency after stroke on a scale ranging from 0 (no symptoms) over 1 (symptoms but no disability), 2 (slight disability), 3 (requires help, but can walk without assistance), 4 (cannot walk without assistance), 5 (bedridden, severe disability, requires constant nursing) to 6 (death) (Kasner 2006). It is part of the usual stroke workup.

Barthel Index (BI): Like the mRS the BI is part of the usual stroke workup. It measures abilities of daily living. The items can be scored from 0 to 15 points maximum, adding up to 0 to 100 points. A high score reflects high independency (Kasner 2006).

Action Research Arm Test (ARAT): The ARAT assesses the range of activity of the UE after stroke. It consists of the subscales grasp, grip, pinch and gross movements which are scored from 0 (no movement) over 1 (movement only partially possible), 2 (movement possible but only with great difficulty or needing much time) to 3 (normal movement), adding up to 57 points maximum. A score with less than 10 points reflects severe impairment (Chen et al. 2012). It is not part of the usual stroke workup.

Stroke Specific Quality Of Life scale (SS-QOL): The SS-QOL measures health related quality of life. It consists of 49 items which are scored from 1 to 5, adding up to 29-245 points. A high score reflects high quality of life (Williams et al. 1999). It is not part of the usual stroke workup.

Beck's Depression Inventory (BDI): The BDI is a depression screening tool consisting of 21 items which are scored from 0 to 3, adding up to 0 to 63 points. A high score reflects high possibility of depression, the threshold for a diagnosis of depression is 10 (Richter et al. 1998). It is not part of the usual stroke workup.

Apart from the clinical tests described above clinical data (e. g. vital parameters, medication etc.) will be collected. In the Universitätsklinikum Tübingen (UKT) this data will be retrieved automatically from the clinic system. In the rehabilitation facilities number and duration of therapies as well as independent training of the patient will be documented and classified according to the type of neurorehabilitative training (e. g., with or without equipment). In addition, therapy-influencing co-factors like support by relatives are registered using a questionnaire with a scale from 0-3 (never/very poor to daily/very good) (see appendix).

Laboratory workup: Routine laboratory workup as part of the usual stroke workup will be collected.

Imaging: For each subject neuroimaging is acquired. If possible and meaningful, MRI is conducted including diffusion weighted imaging (DWI), fluid attenuated inversion recovery (FLAIR) and a Magnetic Prepared-Rapid Gradient Echo (MP-Rage) sequence. The first two sequences are part of the usual stroke workup, the MP-RAGE sequence is added to obtain a 3D anatomical data set for exact assessment of the localization and volume estimation of the stroke lesion.

The MRI images will be acquired at a 1,5 or 3 Tesla MRI scanner in the neuroradiological department of the UKT. The patient is placed in the scanner with earplugs and an emergency ball. Visual and verbal contact to the patient is maintained from the control room. Before scanning, patients are always evaluated by a medical doctor for MRI contraindications.

If an MRI is neither meaningful nor available or there are contraindications, a cranial computed tomography (CT) in the neuroradiological department will be performed. CTs are part of the usual stroke work-up, there will be no additional scanning apart from what is clinically necessary.

Functional MRI (fMRI): fMRI measures the blood-oxygenation-level dependent effect e. g. corresponding to specific task like moving the hand (task-related fMRI). Resting-state MRI determines functional brain networks of synchronized neural activity while the subject is resting (i.e. not performing a task). Resting-state fMRI and task-related fMRI will provide information about functional and effective connectivity, respectively. fMRI is not part of the usual stroke workup and requires additional scanning.

The fMRI images will be acquired at a Siemens 3 Tesla MRI scanner in the MRI Research Center of Tübingen (Department Biomedizinische Magnetresonanz, Prof. Dr. phil. nat. Dipl.-Phys. Klaus Scheffler, Hoppe-Seyler-Str. 3, 72076 Tübingen). The patient is placed in the scanner with earplugs and an emergency ball. Visual and verbal contact to the patient is maintained from the control room. No drugs or contrast agents are used during fMRI examinations.

For the task-related fMRI the patient will be asked to perform stereotypical whole-hand fist closings. Patients are evaluated by a medical doctor for MRI contra-indications and need to give written informed consent before the scan. Based on the work of Wezel et al. (2014), we do not consider dental retainer wires over four teeth at most a contraindication. However, subjects will be informed additionally about current scientific consent and instructed to press the emergency ball in the unexpected case of heating of the retainer wire.

EEG: Resting-state EEG will be obtained using a 21-channel or 64-channel gel filled sintered ring electrode EEG cap (EasyCap, Munich, Germany) using the same optically isolated amplifier as described above (MEGA NeurOne Tesla, Kuopio, Finland). EEG will be recorded with eyes closed and eyes open for three minutes each in the same session in which the TEP and MEPs (described below) are acquired. EEG will always be performed before TMS (needed for TEPs and MEPs). If epileptic potentials are detected in EEG indicating an increased risk of seizure in the patient, TMS will not be conducted.

Electrooculography (EOG): Eye movements will be recorded from additional bipolar channels using the same optically isolated amplifier as for electromyography (EMG) and EEG recordings (MEGA NeurOne Tesla, see above). The EOG data will be used to aid EEG artefact rejection from eye movements and as a behavioral readout in saccade and decision tasks.

TMS: TMS is a technique which evokes action potentials in cortex with a spatiotemporal precision of millimeters and milliseconds. Conventional TMS stimulators (Mag & More, Munich, Germany, Research 100; Magstim 200 als BiStim bzw. 1-4 Quadripulse Option; Magstim Super Rapid Plus) and EEG compatible coils will be used. Experiments will be MRI-guided, using a TMS navigator system (Localite GmbH) to map the exact individual stimulation sites. Subjects will be seated on a comfortable reclining chair with both arms relaxed.

EMG/MEP: Surface EMG will be obtained through an optically isolated battery powered biosignal amplifier (MEGA NeurOne Tesla, see above) using bipolar electrodes from hand muscles (first dorsal interosseous and extensor capri radialis muscles). MEPs are executed with pre-innervation of the target muscle or – if not possible – the contralateral side and maximum stimulator output (if required) to determine if the patient is MEP- or MEP+ (at least 50 µV peak-to-peak amplitude in the target muscle in at least 5 out of 10 consecutive trials). In case of MEP-, a paired-pulse protocol is conducted, which increases the probability to evoke a MEP and consecutively re-classify the subject as MEP+.

EEG/TEP: TEPs will be recorded with a TMS-compatible gel filled sintered ring electrode EEG cap with at least 64 channels (EasyCap, Munich, Germany) using the same optically isolated amplifier as described above (MEGA NeurOne Tesla, see above). During the EEG recordings at least 100 trials of single TMS pulses are applied to the motor hotspot of the ipsilesional M1 with a randomly jittered inter-trial interval of 7–8.0 s with 80% resting motor threshold (RMT). RMT is defined as stimulus intensity needed to evoke MEPs of 50 µV peak-to-peak amplitude in the target muscle in at least 5 out of 10 consecutive trials and will be determined for ipsilesional and contralesional M1. If no MEPs are detectable from the ipsilesional M1, we will use the contralesional M1 for determining RMT and stimulator output and anatomical landmarks like the hand knob for locating the hotspot. To avoid auditory evoked potentials from the clicking noise of the coil patients will wear earplugs. Bone conductions is prevented by placing a thin layer of plastic film between the TMS coil and the EEG cap.

List of measurements which are part of the usual stroke workup:

- Clinical tests: NIHSS, mRS, BI
- Routine laboratory workup
- Imaging: CT or MRI (depending on medical indication)

List of measurements which are <u>not</u> part of the usual stroke workup:

- Clinical tests: FMA for UE and the sensory system, SAFE score, grip strength, Bells Test, AST, ARAT, SS-QOL scale, BDI
- Imaging: fMRI
- Electrophysiological measurements: EEG, MEPs, TEPs

8.5 Endpoints

Primary endpoint: Change in FMA of UE 3 months after the stroke event compared to FMA of UE within the first 25-48 hours after stroke onset.

Secondary end points: Secondary endpoints will be quality of life, independency and range of activity of the UE measured by SS-QOL, mRS, BI and ARAT respectively 3 months after the stroke event compared to the respective values obtained in the acute phase.

8.6 Subject inclusion and exclusion criteria

Inclusion criteria:

- Subject is 18 years or above.
- Subject has an acute stroke affecting one UE (FMA $\leq$ 50).
- Subject understands the study and its procedures and gives informed consent.
- If the subject is not able to give informed consent:
    - The assumed will of the patient is to be determined by the patient's provision (if existing), the health care proxy (if existing) and/or the moral concepts expressed by the patient to close relatives.
    - The legal representative gives informed consent because participation is the assumed will of the patient as assessed by the aforementioned points.

Exclusion criteria:

- Subject is less than 18 years old.
- The subject does not have an acute stroke, or stroke does not affect the UE, or FMA > 50.
- Subject or legal representative cannot give informed consent.
- Patient has an intracranial implant (e.g., aneurysm clips, shunts, stimulators, cochlear implants, or electrodes) or any other metal object within or near the head (excluding the mouth) that cannot be safely removed.
- Subject has a history of any illness that, in the opinion of the study investigator, might confound the results of the study or poses an additional risk to the subject by their participation in the study.
- There is any concern by the investigator regarding the safe participation of the subject in the study, or for any other reason the investigator considers the subject inappropriate for participation in the study.
- Subject is pregnant.

9. Workflow

Stroke Unit:

- Day 1 (0-24 h):

    - Screening: All patients admitted to the SU with acute stroke are screened for participation.
    - Acquiring informed consent from patients respectively their legal representatives (given that participation is in accordance with the assumed will of the patient).
    - Acquiring data set in the acute phase on the SU:
        - Clinical tests: NIHSS*, mRS*, SAFE score
- Day 2 (25-48 h):
    - Neuroimaging (MRI* with DWI, FLAIR and MP-Rage or CT*) (also one day later possible)
    - Clinical tests: grip strength, FMA for UE and sensibility, ARAT, BI*
- Day 3 (49-72 h):
    - Clinical tests: Bells test, AST, BDI, SS-QOL
    - Task-related and resting-state fMRI
    - Neuroimaging (MRI with DWI, FLAIR and MP-Rage or CT) (at the latest)
- Day 4 (73-96 h):
    - EEG
    - MEPs
    - TEPs

Examinations which are part of the usual stroke workup are marked by '*'. For an overview, see the list in the last section of 8.4 Measurement procedures.

Rehabilitation facility:

- On admission: FMA for UE, mRS and BI are acquired
- during the stay:
    - at intervals of 14 days FMA for UE, mRS and BI are obtained
    - number, duration, and type of therapies as well as independent training and therapy-influencing cofactors (e. g. support by relatives) will be documented
- On discharge: FMA for UE, mRS and BI is acquired

After 90 days: FMA for UE, ARAT, BI, mRS and SS-QOL are applied. If the subject is still in rehabilitation, the tests are conducted by the rehabilitation facility. If the subject returned home or was moved to a nursing home, the tests are conducted by the UKT. The way to the clinic and back home will be covered by a commuting accident insurance.

10. Safety precautions

Clinical tests: All clinical tests are conducted by or under the supervision of a qualified medical doctor of the Brain Networks and Plasticity Lab of Prof. Ziemann located in the UKT or a cooperating rehabilitation facility. As indicated in the list in the last section of 8.4 Measurement procedures, NIHSS mRS and BI are part of the usual stroke workup while the rest of the clinical tests are performed for research purposes only. The execution of these additional tests (FMA for UE and the sensory system, SAFE score, grip strength, Bells Test, AST, ARAT, SS-QOL scale, BDI) will take about 1-1.5 h. Since this might be exhausting for stroke patients the tests will be done in separate blocks over a duration of three days to guarantee enough rest and recreation time in between.

The tests planned in the rehabilitation hospital are the FMA for the UE, BI and mRS on admission, at intervals of 14 days and on discharge. The BI is already done routinely in rehabilitation facilities, FMA for UE and the mRS will require about 30 minutes per test session.

In the final examination after 90 days the FMA for UE, ARAT, mRS, BI and SS-QOL will be done in the outpatient department of the UKT, taking probably 1-1,5 h. The way to the clinic and back home will be covered by a commuting accident insurance.

Imaging: MRI or CT are performed by a qualified medical doctor of the department of neuroradiology of the UKT. They are part of the usual stroke workup. fMRI scans are conducted for scientific reasons only and will therefore not be executed and evaluated by a medical doctor of the former mentioned department. Before imaging each patient is screened for contraindications. If the investigator has any doubt that the patient might be not fit enough for scanning, the fMRI will not be performed. The patient is placed in the scanner with earplugs and an emergency ball. For both MRI and CT, visual and verbal contact to the subject is maintained from the control room. The fMRI will take about 1.5 hours including preparation time. The actual scanning will last 30 minutes.

EEG, MEPs, TEPs: All tests will be performed by a qualified medical doctor in the Brain Networks and Plasticity Lab of Prof. Ziemann located in the university hospital. Standard safety precautions to monitor the risk of possible induction of seizures will be followed, according to the present consensus guidelines on safety, ethical considerations, and application of TMS in clinical practice and research Laboratory workup (Rossi et al. 2009). EEG, MEPs and TEPs are not part of the usual stroke workup and thus are conducted for scientific reasons only. EEG and MEPs take about 30 minutes (including preparation). The actual measurements will take about 15 minutes. Since the TEPs are detected by 64-channel-EEG, they require more preparation time, resulting in an expenditure of time of about 2 hours; the recording of the TEPs will take about 20 minutes. If the investigator has any doubt that the patient might not fit enough for TEPs, they will not be performed.

MEPs and TEPs are not possible without TMS. As mentioned above, a potential risk of TMS are seizures, which is normally 0.3 in 1000 TMS sessions (Lerner et al. 2019). However, since stroke leaves structural brain lesion the risk of seizures is increased compared to healthy controls (0.83 in 1000 TMS sessions in subjects with increased risk of seizures stimulated with a single- or paired-pulse protocol like ours (Lerner et al. 2019)), EEG will always be conducted before TMS in this study. If there is any indication for increased risk of seizures (spikes, sharp waves etc.) TMS will not be conducted.

Although this is a purely observational study without any dangerous interventions, we are aware, that we request a lot of time and dedication from the participating patients. The additional clinical, imaging and electrophysiological tests require at least 1.5-2 hours respectively 4.5-5 hours (if TEPs and fMRI are also done). To make participating as less exhausting as possible we implemented the following policies:

- Clinical tests are conducted over a course of three days. This might be one block a day (with a duration of 30 minutes) or two blocks each day (in the morning and in the afternoon) with a duration of 15 minutes.
- fMRI and TEPs, which are – in our view – by far the most strenuous examinations, will be only conducted in relatively fit patients. If there is any doubt about the patient's fitness regarding fMRI and TEPs, these tests will not be performed. The affected patients are not excluded from the study. We expect that 200-250 out of 500 will be able to take part in TEPs and fMRI.
- If fMRI and TEPs are not performed, patients do not have to leave the SU for the study, since the clinical tests, the 21-channel EEG and the MEPs are conducted at the bedside. (Of course,

the patients will leave the SU for an CT or MRI scan, but those are medically indicated and not for scientific research only.)

- Instrument-based diagnostics (like EEG or imaging) will be done on separate days to ensure that the patients get enough rest between them.

11. Objectives and hypotheses

The scientific goal of the present study is to identify markers in the acute phase of stroke that will predict recovery of UE function during neurorehabilitative treatment, and to predict which neurorehabilitative treatment is most suited in a given patient to achieve optimal outcome using machine learning algorithms.

12. Study population definition

We aim to include all patients with acute stroke affecting the UE (FMA $\leq$ 50) on our SU. Other symptoms like aphasia or neglect are no reason for exclusion since we intend to include as many patients as possible to capture the whole spectrum of stroke from mild to severe. Especially the last case, the inclusion of severely affected patients, is of utmost importance in our view. Due to their grave impairments they have the greatest need for neurorehabilitation; at the same time, this group of patients is the most vulnerable because of their preexisting comorbidities and conditions coming with immobility e. g. pneumonia. A personalized treatment would meet their need for intense rehabilitation while providing enough recreation time since unnecessary, ineffective rehabilitation could be omitted.

In particular among those severely affected stroke patients will be some who are not able to give informed consent due to aphasia or delirium. Since this group is probably the one benefiting the most from the results of this study, we would like to include them nevertheless, given the premise, the participation is in accordance with the assumed will of the patient.

The assumed will of the patient will be determined by the patient's provision (if existing), the health care proxy (if existing) and/or the moral concepts expressed by the patient to close relatives (see "Feststellung des mutmaßlichen Willens des Patienten/der Patientin" in the appendix). If it is to be assumed that the participation in this study is in accordance with the patient's will we will ask the legal representatives for consent. It there is any doubt about the patient's willingness to participate in the study, he or she will not be recruited.

If the patient regains his or her ability to give informed consent in the course of the study (90 days after stroke event), he or she will be informed about his or her participation and asked for informed consent. If the patient decides against taking part in the study, he or she has the right to request deletion of all so far collected data and participation ends immediately.

If the patient regains his or her ability to give consent after the course of 90 day, that is, after completing the study, he or she can request the patient information at any time and – if desired – revoke his or her agreement to participate and request the deletion of all collected data.

13. Statistical analysis

We will use machine learning algorithms to predict the primary end point (i.e. change in FMA 90 days after the stroke event) as a function of the clinical tests, clinician-specified features extracted from MRI/EEG data acquired right after the stroke event and the rehabilitation program. Model development will start when data from 100 patients have been acquired and will continue until 300 patients have been reached. Before model development with subject data starts, algorithms will be tested with artificial data sets including sets with missing data. Effective algorithms on simulated data-sets with missing data will be used as candidate-algorithms for analysis of the empirical data.

To cope with the dimensionality of the problem, we will use lasso-regularized linear regression to select a sparse subset of the potentially correlated features. We will use a nested-crossvalidation setup to tune the regularization strength via the 1SE-rule (Hastie et al. 2009) and obtain estimates of the fraction of the explained variance of the total variance in the primary end point on data not seen during model training. The final 200 patients will serve as a true hold-out test set to assess the predictive performance of the model. If the linear model proves insufficient or unsatisfying, we will resort to non-linear regression models such as Generalized Additive Models (GAMs), which allow flexible nonlinear transformations of individual features or pairs of features (Wood 2017). Models for alternative endpoints will be built as well.

14. Risks and benefits

MRI is a daily-applied diagnostic method. Harmful effects of magnetic fields and radio frequency are not known, as long as the standardized MRI inclusion/exclusion criteria are obeyed. CT is an imaging method using X-ray and thus radioactive radiation. However, imaging is an obligate part of stroke workup, which is why participating in the present study will not lead to further CT imaging and radiation exposure apart from the imaging performed anyway.

The most severe acute adverse effect for TMS is the risk of the induction of seizures. However, in the more than 1,000 papers published using TMS between 1999-2008, only six seizures were reported, one of which may have been a pseudo seizure, two could have been syncopes, and the remaining three occurred using a high intensity stimulation protocol under pro-epileptogenic medication or following sleep-deprivation (Rossi et al. 2009). A more recent study has confirmed that the risk of seizure induction by TMS is very low, only in 0.3 of 1000 TMS sessions with healthy subjects seizures occurred (Lerner et al. 2019). However, since stroke leaves structural brain lesion the risk of seizures is increased compared to healthy controls (0.83 in 1000 TMS sessions in subjects with increased risk of seizures stimulated with a single- or paired-pulse protocol like ours (Lerner et al. 2019)). Therefore, EEG will always be conducted before TMS in this study. If there is any indication for increased risk of seizures (spikes, sharp waves etc.) TMS will not be conducted.

In addition to the risk of seizures, TMS-induced headache is a minor risk but is usually light or moderate in intensity and self-limiting.

EEG, EMG and EOG are passively recorded electrical biosignals and have no side-effects; irritation to the skin may be provoked after application of the electrode cream.

For the laboratory workup taking a blood samples is necessary. However, since laboratory tests are part of the usual stroke workup, participating in the present study will not lead to further blood samples apart from the blood samples taken anyway. However, patients will be offered to give a blood sample to the biobank. This would be indeed an additional sample and patients will be separately informed about this possibility. This sample will be taken only after the broad consent form of the UKT has been signed.

Although this is a purely observational study without any dangerous interventions, we are aware, that we request a lot of time and dedication from the participating patients which might be exhausting for some of them. To ensure enough recreation time between procedures, clinical tests are conducted in blocks over three days and instrumental-based diagnostics will be done on separate days.

The overall risk for subjects participating in this trial therefore can be considered very low. Many of the procedures are performed in any case as part of the stroke workup independently of the present study. Participating subjects will have no direct benefit from this study.

It is expected that the present study will lead to new evidence regarding the improvement of stroke outcome by personalizing rehabilitation treatment and will broaden the existing knowledge about the physiological basis of stroke and recovery.

15. Data analysis, storage, and safety

Data acquisition and storage is performed in accordance with the regulatory requirements of the DSGVO directives. Case report forms or other data which might be photocopied for verification by authorized persons, e.g. the Independent Ethics Committee, will be pseudonymized, i.e. they will not contain the name of the subjects but only their unique identification code. Publication of data, e.g., in the form of a scientific oral presentation or publication will only contain anonymized data.

The clinical data will be stored on a REDCap databank. The clinical tests are filled out directly in the databank itself or on paper. If the latter is the case, these documents are stored together with informed consent and the signed data protection declaration in a closed locker which can only be accessed by authorized stuff.

Electrophysiological data, clinical imaging and laboratory data will be stored and processed on the secured storage area network of the UKT. The results of the analyzed data will then be inserted in the REDCap databank.

The fMRI data will be stored and analyzed on the cluster of Biomedizinische Magnetresonanz (run by Bernd Kardatzki, part of the UKT). The results of the analyzed data will then be inserted in the REDCap databank.

The cooperating rehabilitation hospitals nominated staff members responsible for data collection and documentation. These documentalists have access to the REDCap databank via a browser-based webpage. Their REDCap accounts are limited to their respective rehabilitation facility, in other words, each documentalist has only access to the data of their own patients. (The same rule applies for UKT members with exception for the investigators.)

Rehabilitation procedures are regularly planned and documented in a program called GTP on the system of the respective rehabilitation facility. From there the rehabilitation treatment will be transferred to the REDCap databank by the documentalists. Clinical tests conducted in the

rehabilitation hospital (mRS, BI and FMA for UE, questionnaire about therapy influencing factors) are either directly filled in on the website of the REDCap databank or on paper from which the data is then inserted in the databank by the documentalists. The sheet of paper is stored in the medical record of the patient.

The data exchange between the UKT and the cooperating rehabilitation facilities is fixed by contract about joint controllership in a clinical study under the directive of Art. 26 of the DSGVO.

Subjects' files will be saved using codes in order to protect their privacy. Volume cloning ensures instantaneous data backup. All data will be stored for a minimum of 10 years to enable data reanalysis and sustained availability.

The study protocol was checked and approved by the data protection officer of the UKT.

Literaturverzeichnis

Brott, Thomas; Adams Jr., Harold P.; Olinger, Charles P.; Marler, John R.; Barsan, William G.; Biller, Jose et al. (1989): Measurements of acute cerebral infarction: a clinical examination scale. In: *Stroke* 20 (7), S. 864–870, zuletzt geprüft am 15.06.2020.

Casali, Adenauer G.; Grosseries, Olivia; Rosanova, Mario; Boly, Melanie; Sarasso, Simone; Casali, Karina R. et al. (2013): A Theoretically Based Index of Consciousness Independent of Sensory Processing and Behavior. In: *Sci Transl Med* 14 (5), zuletzt geprüft am 30.06.2020.

Chen, Hui-fang; Lin, Keh-chung; Wu, Ching-yi; Chen, Chia-ling (2012): Rasch validation and predictive validity of the action research arm test in patients receiving stroke rehabilitation. In: *Archives of physical medicine and rehabilitation* 93 (6), S. 1039–1045. DOI: 10.1016/j.apmr.2011.11.033.

Compston, Alastair (2010): Aids to the investigation of peripheral nerve injuries. Medical Research Council: Nerve Injuries Research Committee. His Majesty's Stationery Office: 1942; pp. 48 (iii) and 74 figures and 7 diagrams; with aids to the examination of the peripheral nervous system. By Michael O'Brien for the Guarantors of Brain. Saunders Elsevier: 2010; pp. 8 64 and 94 Figures. In: *Brain : a journal of neurology* 133 (10), S. 2838–2844. DOI: 10.1093/brain/awq270.

Drozdowska, Bogna A.; Singh, Sarjit; Quinn, Terence J. (2019): Thinking About the Future: A Review of Prognostic Scales Used in Acute Stroke. In: *Frontiers in neurology* 10, S. 274. DOI: 10.3389/fneur.2019.00274.

Fanciullacci, Chiara; Bertolucci, Federica; Lamola, Giuseppe; Panarese, Alessandro; Artoni, Fiorenzo; Micera, Silvestro et al. (2017): Delta Power Is Higher and More Symmetrical in Ischemic Stroke Patients with Cortical Involvement. In: *Frontiers in human neuroscience* 11, S. 385. DOI: 10.3389/fnhum.2017.00385.

Ferber, Susanne; Karnath, Hans-Otto (2002): Neglect-Tests im Vergleich - welche sind geeignet? In: *Zeitschrift für Neuropsychologie* 13 (1), S. 39–44. DOI: 10.1024//1016-264X.13.1.39.

Finnigan, Simon; van Putten, Michel J. A. M. (2013): EEG in ischaemic stroke: quantitative EEG can uniquely inform (sub-)acute prognoses and clinical management. In: *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology* 124 (1), S. 10–19. DOI: 10.1016/j.clinph.2012.07.003.

Gladstone, David J.; Dannels, Cynthia J.; Black, Sandra E. (2002): The Fugl-Meyer Assessment of Motor Recovery after Stroke: A Critical Review of Its Measurement Properties 16, S. 232–240, zuletzt geprüft am 15.06.2020.

Grefkes, Christian; Nowak, Dennis A.; Eickhoff, Simon B.; Dafotakis, Manuel; Küst, Jutta; Karbe, Hans; Fink, Gereon R. (2008): Cortical connectivity after subcortical stroke assessed with functional magnetic resonance imaging. In: *Annals of neurology* 63 (2), S. 236–246. DOI: 10.1002/ana.21228.

Hastie, Trevor; Tibshirani, Robert; Friedman, Jerome (2009): The elements of statistical learning, second edition. Data mining, inference, and prediction. 2nd ed. New York: Springer (Springer Series in Statiscal).

Hatanu, Adina; Iancu, Mihaela; Balasa, Rodica; Maier, Smaranda; Dobreanu, Minodora (2018): Predicting functional outcome of ischemic stroke patients in Romania based on plasma CRP, sTNFR-1, D-Dimers, NGAL and NSE measured using a biochip array. In: *Acta Pharmacologica Sinica* 39, S. 1228–1236, zuletzt geprüft am 01.07.2020.

He, Lanying; Wang, Jian; Dong, Weiwei (2018): The clinical prognostic significance of hs-cTnT elevation in patients with acute ischemic stroke. In: *BMC neurology* 18 (1), S. 118. DOI: 10.1186/s12883-018-1121-5.

Heo, JoonNyung; Yoon, Jihoon G.; Park, Hyungjong; Kim, Young Dae; Nam, Hyo Suk; Heo, Ji Hoe (2019): Machine Learning-Based Model for Prediction of Outcomes in Acute Stroke. In: *Stroke* 50 (5), S. 1263–1265. DOI: 10.1161/STROKEAHA.118.024293.

Kasner, Scott E. (2006): Clinical interpretation and use of stroke scales. In: *The Lancet Neurology* 5 (7), S. 603–612. DOI: 10.1016/S1474-4422(06)70495-1.

Kim, Bokkyu; Winstein, Carolee (2017): Can Neurological Biomarkers of Brain Impairment Be Used to Predict Poststroke Motor Recovery? A Systematic Review. In: *Neurorehabilitation and neural repair* 31 (1), S. 3–24. DOI: 10.1177/1545968316662708.

Kroker, Carsten (2006): Aphasie-Schnelltest (AST). Ein standardisierter Test für die Differentialdiagnose ; Aphasie - keine Aphasie - Dysarthrie in der Akutphase. 3. Aufl. Idstein: Schulz-Kirchner (Das Gesundheitsforum).

Leão, Maria Teresa; Naros, Georgios; Gharabaghi, Alireza (2020): Detecting poststroke cortical motor maps with biphasic single- and monophasic paired-pulse TMS. In: *Brain stimulation* 13 (4), S. 1102–1104. DOI: 10.1016/j.brs.2020.05.005.

Lerner, Adam J.; Wassermann, Eric M.; Tamir, Diana I. (2019): Seizures from transcranial magnetic stimulation 2012-2016: Results of a survey of active laboratories and clinics. In: *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology* 130 (8), S. 1409–1416. DOI: 10.1016/j.clinph.2019.03.016.

Makris, Konstantinos; Haliassos, Alexander; Chondrogianni, Maria; Tsivgoulis, Georgios (2018): Blood biomarkers in ischemic stroke: potential role and challenges in clinical practice and research. In: *Critical reviews in clinical laboratory sciences* 55 (5), S. 294–328. DOI: 10.1080/10408363.2018.1461190.

Maruyama, Kenji; Uchiyama, Shinichiro; Shiga, Tsuyoshi; Iijima, Mutsumi; Ishizuka, Kentaro; Hoshino, Takao; Kitagawa, Kazuo (2017): Brain Natriuretic Peptide Is a Powerful Predictor of Outcome in Stroke Patients with Atrial Fibrillation. In: *Cerebrovascular diseases extra* 7 (1), S. 35–43. DOI: 10.1159/000457808.

Park, Chang-hyun; Chang, Won Hyuk; Ohn, Suk Hoon; Kim, Sung Tae; Bang, Oh Young; Pascual-Leone, Alvaro; Kim, Yun-Hee (2011): Longitudinal changes of resting-state functional connectivity during motor recovery after stroke. In: *Stroke* 42 (5), S. 1357–1362. DOI: 10.1161/STROKEAHA.110.596155.

Puig, Josep; Blasco, Gerard; Alberich-Bayarri, Angel; Schlaug, Gottfried; Deco, Gustavo; Biarnes, Carles et al. (2018): Resting-State Functional Connectivity Magnetic Resonance Imaging and Outcome After Acute Stroke. In: *Stroke* 49 (10), S. 2353–2360. DOI: 10.1161/STROKEAHA.118.021319.

Rehme, Anne K.; Eickhoff, Simon B.; Wang, Ling E.; Fink, Gereon R.; Grefkes, Christian (2011): Dynamic causal modeling of cortical activity from the acute to the chronic stage after stroke. In: *NeuroImage* 55 (3), S. 1147–1158. DOI: 10.1016/j.neuroimage.2011.01.014.

Richter, Paul; Werner, Joachim; Heerlein, Andres; Kraus, Alfred; Sauer, Heinrich (1998): On the Validity of the Beck Depression Inventory. A Review. In: *Psychopathology* 31 (3), S. 160–168, zuletzt geprüft am 16.06.2020.

Rosanova, M.; Fecchio, M.; Casarotto, S.; Sarasso, S.; Casali, A. G.; Pigorini, A. et al. (2018): Sleep-like cortical OFF-periods disrupt causality and complexity in the brain of unresponsive wakefulness syndrome patients. In: *Nature communications* 9 (1), S. 4427. DOI: 10.1038/s41467-018-06871-1.

Rossi, Simone; Hallett, Mark; Rossini, Paolo M.; Pascual-Leone, Alvaro (2009): Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. In: *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology* 120 (12), S. 2008–2039. DOI: 10.1016/j.clinph.2009.08.016.

Saber, Hamidreza; Somai, Melek; Rajah, Gary B.; Scalzo, Fabien; Liebeskind, David S. (2019): Predictive analytics and machine learning in stroke and neurovascular medicine. In: *Neurological research* 41 (8), S. 681–690. DOI: 10.1080/01616412.2019.1609159.

Sheorajpanday, Rishi V. A.; Nagels, Guy; Weeren, Arie J. T. M.; van Putten, Michel J. A. M.; Deyn, Peter P. de (2011): Quantitative EEG in ischemic stroke: correlation with functional status after 6 months. In: *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology* 122 (5), S. 874–883. DOI: 10.1016/j.clinph.2010.07.028.

Stinear, Cathy M.; Byblow, Winston D.; Ackerley, Suzanne J.; Smith, Marie-Claire; Borges, Victor M.; Barber, P. Alan (2017): PREP2: A biomarker-based algorithm for predicting upper limb function after stroke. In: *Annals of clinical and translational neurology* 4 (11), S. 811–820. DOI: 10.1002/acn3.488.

Thiel, Alexander; Vahdat, Shahabeddin (2015): Structural and resting-state brain connectivity of motor networks after stroke. In: *Stroke* 46 (1), S. 296–301. DOI: 10.1161/STROKEAHA.114.006307.

Tscherpel, Caroline; Dern, Sebastian; Hensel, Lukas; Ziemann, Ulf; Fink, Gereon R.; Grefkes, Christian (2020): Brain responsivity provides an individual readout for motor recovery after stroke. In: *Brain : a journal of neurology*. DOI: 10.1093/brain/awaa127.

van Kuijk, Annette A.; Pasman, Jaco W.; Hendricks, Henk T.; Zwarts, Machiel J.; Geurts, Alexander C. H. (2009): Predicting hand motor recovery in severe stroke: the role of motor evoked potentials in relation to early clinical assessment. In: *Neurorehabilitation and neural repair* 23 (1), S. 45–51. DOI: 10.1177/1545968308317578.

VanGilder, Reyna L.; Davidov, Danielle M.; Stinehart, Kyle R.; Huber, Jason D.; Turner, Ryan C.; Wilson, Karen S. et al. (2014): C-reactive protein and long-term ischemic stroke prognosis. In: *Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia* 21 (4), S. 547–553. DOI: 10.1016/j.jocn.2013.06.015.

Wezel, Joep; Kooij, Bert Jan; Webb, Andrew G. (2014): Assessing the MR compatibility of dental retainer wires at 7 Tesla. In: *Magnetic resonance in medicine* 72 (4), S. 1191–1198. DOI: 10.1002/mrm.25019.

Williams, Linda S.; Weinberger, Morris; Harris, Lisa E.; Clark, Daniel O.; Biller, Jose (1999): Development of a Stroke-Specific Quality of Life Scale. In: *Stroke* 30, S. 1362–1369, zuletzt geprüft am 15.06.2020.

Wood, Simon N. (2017): Generalized additive models. An introduction with R. Second edition. Boca Raton: CRC Press (Chapman & Hall/CRC texts in statistical science series).

Zeiler, Steven R. (2019): Should We Care About Early Post-Stroke Rehabilitation? Not Yet, but Soon. In: *Current neurology and neuroscience reports* 19 (3), S. 13. DOI: 10.1007/s11910-019-0927-x.

Appendix

Einflussfaktoren auf den Rehabilitationsverlauf

Interkurrente Erkrankung: 0: nein; 1: ja

Eigentrainingsanteil

0	1	2	3
nie	Selten (bis 2x pro Wo)	Oft (3-5x pro Wo)	täglich

Training mit Hilfe von Angehörigen

0	1	2	3
nie	Selten (bis 2x pro Wo)	Oft (3-5x pro Wo)	täglich

Verhältnis des Patienten zu seinem (Ergo-)Therapeuten (aus Pat.-sicht)

0	1	2	3
Schlecht bis sehr schlecht	Akzeptabel bis zufriedenstellend	Gut	Sehr gut

Ehrgeiz und Motivation

0	1	2	3
Fast kein / keine	Wenig (muss von extern motiviert werden)	Mäßig bis gut (muss selten motiviert werden)	Gut bis sehr gut (braucht keine externe Motivation)

Universitätsklinikum Tübingen

Neurologische Klinik

Abt. Neurologie mit Schwerpunkt neurovaskuläre Erkrankungen

Ärztl. Direktor: Prof. Dr. med. U. Ziemann

14.03.2021

Feststellung des mutmaßlichen Willens des Patienten / der Patientin

Bei dem Patienten / der Patientin

……., geb. ……..

wird der mutmaßliche Patientenwille anhand

☐ einer Patientenverfügung vom …….. festgehalten.

☐ einer Vorsorgevollmacht vom ……festgehalten. Vorsorgebevollmächtigter ist

……

☐ Es liegt eine gesetzliche Betreuung vor: Gesetzlicher Betreuer ist

……

☐ Die Entscheidung über den mutmaßlichen Patientenwillen erfolgt anhand seines vor der Erkrankung geäußerten Wertevorstellungen gegenüber seinen nahen Angehörigen:

……

Datum Unterschrift Prüfarzt/ärztin