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New Technologies and Concepts for Rehabilitation in the Acute Phase of Stroke: A Collaborative Matrix

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Key Words
Stroke · Rehabilitation · Functional electrical stimulation · Arm robot-assisted therapy · Virtual reality · Mirror neuron

Abstract
The process of developing a successful stroke rehabilitation methodology requires four key components: a good understanding of the pathophysiological mechanisms underlying this brain disease, clear neuroscientific hypotheses to guide therapy, adequate clinical assessments of its efficacy on multiple timescales, and a systematic approach to the application of modern technologies to assist in the everyday work of therapists. Achieving this goal requires collaboration between neuroscientists, technologists and clinicians to develop well-founded systems and clinical protocols that are able to provide quantitatively validated improvements in patient rehabilitation outcomes. In this article we present three new applications of complementary technologies developed in an interdisciplinary matrix for acute-phase upper limb stroke rehabilitation – functional electrical stimulation, arm robot-assisted therapy and virtual reality-based cognitive therapy. We also outline the neuroscientific basis of our approach, present our detailed clinical assessment protocol and provide preliminary results from patient testing of each of the three systems showing their viability for patient use.

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Introduction

Stroke results in several neurological impairments which often severely reduce patient ability to perform activities of daily living (ADL) in both the short and long term. To individual patients, however, the assessments of impairments performed by attending physicians may be less important than maintaining or restoring premorbid daily-life functions. This is particularly true for upper extremity function and especially for skilled tool use. Constraint-induced movement therapy is a well-accepted, evidence-based approach for the chronic stage following a stroke [1, 2]. However, the optimal type of therapy for arm and hand function in the acute stage is still unclear, although a variety of treatment concepts has been defined [3].

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Evidence from animal trials suggests that early initiation of therapy favorably influences efficacy of rehabilitation. In the early post-stroke stages the brain already shows adaptive plasticity in within-system pathways [4, 5], and the brain displays elevated sensitivity to rehabilitative experience. Also, there is evidence of a correlation between early initiation of rehabilitation and better functional outcome as assessed by the Barthel index [6]. Other critical factors for sensorimotor therapy to induce long-term brain plasticity and improve functional outcomes are that the therapy is intensive [7], highly repetitive [8], task-oriented [9] and rewarded. This has been shown in a longitudinal study where therapy was applied early in a repetitive, task-oriented scenario to significantly improve long-term functional outcomes [10, 11]. Other experiments with healthy animal and human subjects suggest that repetitive task-oriented exercise alone will not increase cortical plasticity; rather, some degree of motor learning is required [12, 13] such as that experienced by stroke patients undergoing rehabilitation.

These threads of evidence all point towards the need to develop arm and hand therapies for acute-phase stroke patients that are intensive, repetitive and oriented towards ADL. The best methods and technologies to be used are as yet unknown and likely to vary between patients. In this study we are applying new rehabilitation technologies developed in close collaboration with clinical, engineering and computer science groups interconnected in a 'Rehabilitation Technology Matrix' within the Swiss National Center for Competence in Research in 'Neural Plasticity and Repair'.

Treatment Rationale and Goals

The primary goal of our approach is the multimodal reactivation of sensorimotor mechanisms that are part of the disrupted motor program by stimulation of undamaged regions which project directly or indirectly to sensorimotor areas. At the lowest level, we achieve this by providing the afferent proprioceptive feedback to the central nervous system (CNS) that would be present during normal active movement execution, thus closing the motor control loop. At a higher level, we also aim to recruit motor planning and execution areas by embedding the movements in task-oriented scenarios. At the highest level, we can also stimulate motor planning areas by directing patient attention to a task and encouraging conceptual rehearsal of intended movements [14]. Simultaneously, we activate the action recognition system through visual input simulating the desired movement to provide feedback consistent with correct movement execution. Bilateral training using these techniques has also been shown to increase activation in the motor cortex during the post-stroke acute phase [15] in contrast to the chronic phase, where constraint-induced therapy is the appropriate choice. Coupled bimanual coordination theory postulates that learning involves development of coordinative structures as the centrally linked upper extremities function together in solving motor tasks [16].

The main secondary goal of our approach is to increase activity of the paretic limb through early, intensive and rewarded training of daily living functions, thereby motivating the patient to regain functional independence. The technologies we are deploying can play a key role in this process by replacing the physical strength of the therapist, providing for semiautomatic, objective performance evaluation, and/or enabling partially or completely unsupervised training. Additional benefits of this training regime include the elimination of nonuse patterns of the affected limb through regular daily activity, prevention of compensatory maladaptive strategies, and avoidance of secondary acquired abnormal movements.

New Approaches – Technology Overview

Conventional physiotherapy uses the decades-old method of peripheral manipulation performed by therapists, possibly with the help of mechanical devices or supports. The new methods we are investigating in this study – functional electrical stimulation (FES), exoskeleton arm robot (ARMin) therapy and cognitive virtual-reality (VR)-based therapy – build on this methodology by assisting the therapist with the manipulation and measurement processes, and providing new possibilities for engaging the patient's peripheral nervous system and CNS (PNS/CNS). The three systems mainly differ from each other in the primary methods used to stimulate the PNS/CNS, ranging from peripheral manipulation (ARMin) through direct surface peripheral muscle stimulation (FES) to CNS stimulation (cognitive VR). These differences are summarized in table 1. In the following sections we describe each of the technologies in more detail.

Functional Electrical Stimulation

FES applies bursts of high-intensity electrical pulses via surface (transcutaneous) electrodes to create action poten-

Table 1. Comparison of rehabilitation technologies

	FES	ARMin	Cognitive VR
Movement control	system and patient, assistance possible, help-arm support	system and patient robot arm support	patient only table arm support
Movement range	whole upper limb	proximal (hand planned)	whole upper limb
Data collection	data glove	force/torque and position sensors on robot arm	digital compass, accelerometer, visual tracking, data glove
Task type	real daily activities unilateral	games and real daily activities unilateral	games and simulated daily activities bilateral
Task evaluation	subjective human assessment	objective software-based	objective software-based
Nervous system stimulation	specific external muscle stimulation plus observation of own arm (unilateral) afferent proprioception	peripheral limb manipulation plus observation of target stimuli afferent proprioception	central bilateral (virtual action observation via mirror neurons) afferent proprioception if patient able to move
Unit cost	low	high	low

tials in stimulated nerves, which cause muscle contractions. The Compex Motion stimulator [17, 18] can be programmed to generate any arbitrary stimulation sequence that can be controlled and regulated. Each stimulator has four output channels; up to four channels (muscle groups) can be stimulated at a time. The stimulation sequences are stored on readily exchangeable memory chip-cards.

With this system we artificially generate muscle contractions required to perform a reaching and grasping task in subjects who have lost voluntary control of these muscles. As different stroke patients present with different disability, to perform a reaching and grasping task we program the Compex Motion stimulator according to the patient's individual needs with regard to their lost or preserved motor function, respectively. Electrode placement for elbow and finger extension is illustrated in figure 1.

Since we include patients with severe paresis a help-arm is used to partially balance the force of gravity on the arm. For hemiplegic patients, a typical combination of stimulated muscles is as follows: anterior deltoid muscle, triceps, extrinsic finger extensors, and extrinsic finger flexors. For tetraplegic patients, normally only distal muscles are stimulated, i.e. finger extensors, finger flexors, and thumb adductor. Depending on the decision of the therapists agonistic and antagonistic muscles can be stimulated. In principle, the method can be applied to subjects with severe spasticity. In order to overcome spasticity we apply pulses that have short pulse durations and therefore preferentially activate efferent nerves and not the afferents that trigger hypertonic antagonist muscles [19]. However, we start with the FES training in the very acute state, in which the subjects have not yet developed severe spasticity.

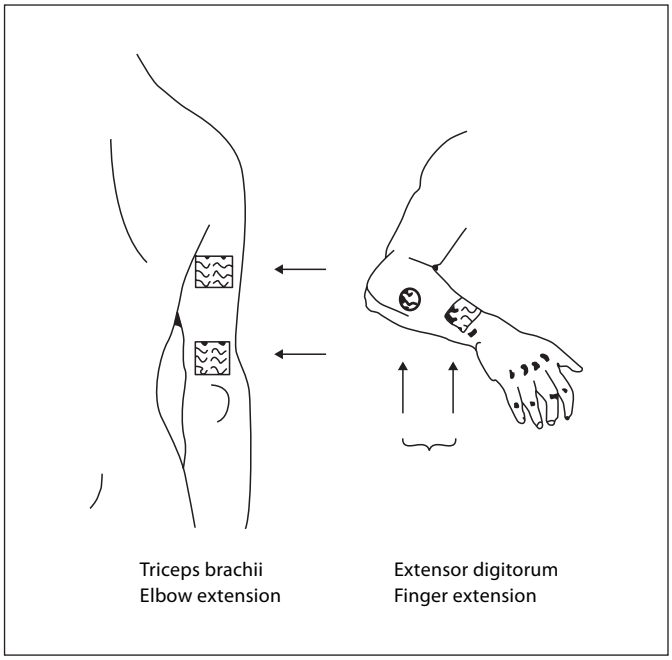

Fig. 1. Electrode placement for functional electrode stimulation to extend the elbow (left) and finger (right).

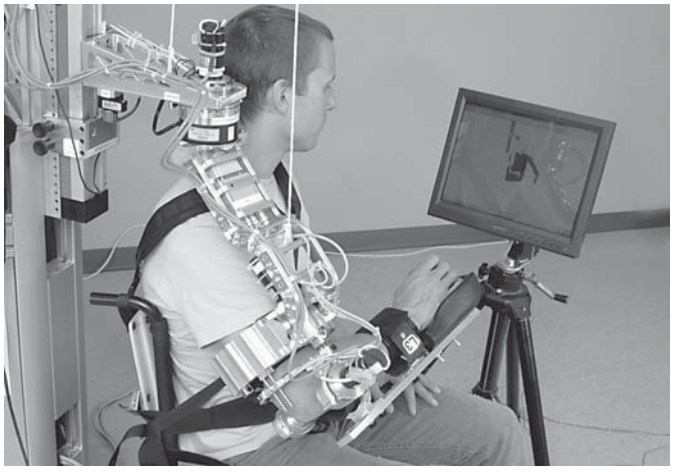

Fig. 2. ARMin robot with a healthy test subject.

Robot-Assisted Rehabilitation and Measurement (ARMin)

Rationale

Manually assisted movement training has several limitations. The training is labor-intensive, and, therefore, training duration is usually limited by personnel shortage and fatigue of the therapist, not by that of the patient. The disadvantageous consequence is that the training sessions are shorter than required to gain an optimal therapeutic outcome. Furthermore, manually assisted movement training lacks repeatability and objective measures of patient performance and therapy progress.

In contrast, with automated, i.e. robot-assisted, arm training the duration and number of training sessions can be increased, while reducing the number of therapists required per patient. Long-term automated therapy appears to be the only way to make intensive arm training affordable for clinical use. In the future, one therapist may be able to train 2 or more patients simultaneously. Thus, personnel costs can be significantly reduced. Furthermore, the robot provides quantitative measures, thus, supporting the evaluation of the rehabilitation progress.

Robot System Design

The robot is mounted to the wall with the patient sitting beneath (fig. 2). The patient's torso is fixed to the wheelchair with straps. A semiexoskeleton solution was selected for the mechanical structure of the robot. The distal part of the robot is characterized by an exoskeleton structure, with the patient's forearm and upper arm placed inside two shells moving the elbow joint. The upper arm is connected to an end effector-based structure moving the shoulder in three degrees of freedom. A six-axis force sensor and four position sensors enable the robot to work in different patient-interactive control modes. The robot is designed primarily for the rehabilitation of incomplete spinal cord-injured and stroke patients.

Therapy Modes

ARMin allows three different therapy modes: movement therapy, ADL therapy and game therapy. The goal of *movement therapy* is to prevent joint degeneration and to preserve joint mobility. In this mode, the therapist first guides the human arm together with the robot. The robot stores the movement and then repeats it with adjustable velocity. In *ADL therapy* the subject can perform different tasks such as filling a virtual glass of water, grasping it and moving it towards the mouth (fig. 3). The purpose of *game therapy* is to motivate the patient with simple games presented by an audiovisual display. In one game the user can move a virtual hand to intercept a ball which is rolling down a virtual plane (fig. 3). The robot supports the patient with just as much force as is needed. If the patient is not able to intercept the ball, the robot guides the patient's arm with an adjustable force right before interception.

VR-Based Interactive Cognitive Therapy

The VR-based interactive cognitive therapy system is based on the idea that observing an action with intent to imitate engages similar neural circuitry to that used in actually performing an action – the so-called 'mirror neuron' hypothesis [14]. Indeed, there is evidence that such observation may even induce cortical plasticity under certain conditions [20]. In a rehabilitation setting, it thus seems reasonable that a system capable of appropriately stimulating the action observation system could encourage plasticity and repair during the post-stroke acute phase.

Our interactive multimedia system uses low-cost input devices such as consumer-grade data gloves (P5 data glove, Essential Reality, New York, N.Y., USA) and digital compasses (HMR3300, Honeywell/Digi-Key Corp., Thief River Falls, Minn., USA) linked to a multi-user three-dimensional virtual environment (Torque, GarageGames, Oreg., USA) with visual and audio outputs.

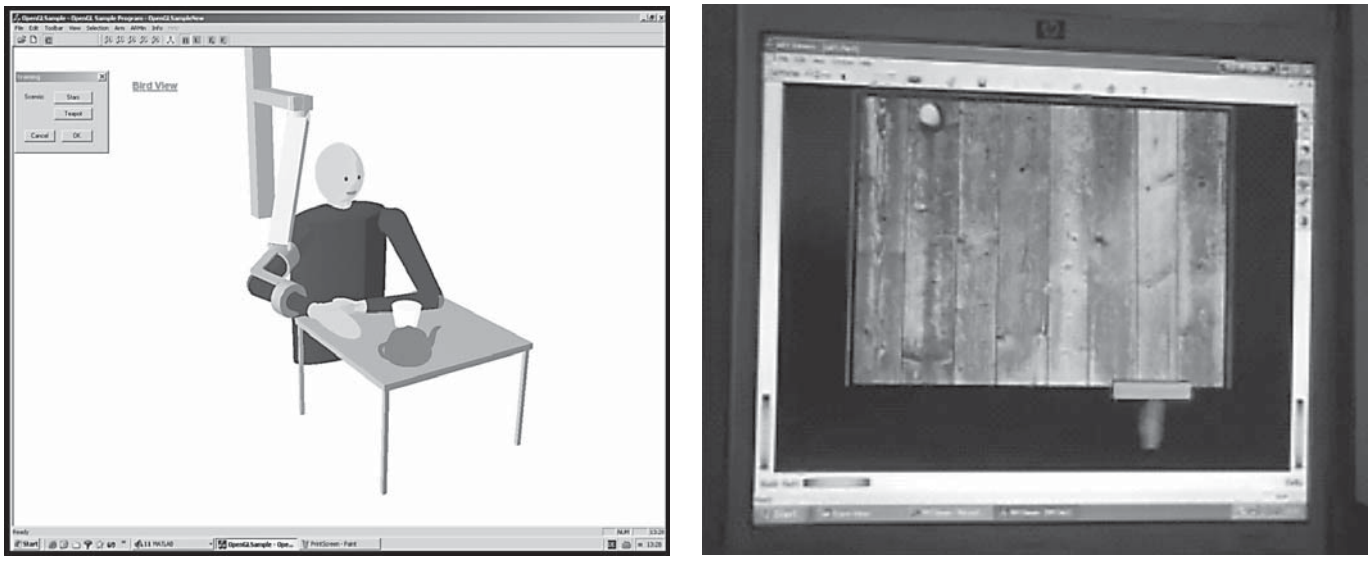

Fig. 3. Visual scenarios for ADL therapy mode (left) and game mode (right).

The system hosts a set of rehabilitation scenarios which are customizable to individual patient needs. The different scenarios provide a graded training program of reaching and grasping for each patient, with on-line quantitative feedback about patient performance for enhancing motivation and monitoring patient progress. The initial scenarios being tested, in order of increasing difficulty according to patient progress, are: (1) hitting – intercept virtual balls moving along a surface towards the patient by moving the arms; (2) catching – intercept objects, with the additional constraint of 'catching' them using the data gloves, and (3) grasping – move hands towards a virtual object, pick up the object, move it to a target location and release it.

In each scenario the patient sits in a chair with his/her arms on a table (fig. 4). The display is designed so that a three-dimensional rendering of two virtual arms appears in a similar orientation to the patient's real arms. Hand and arm movements detected by the input devices are mapped onto the movements of the virtual arms. This mapping can be adjusted by the therapist, and takes the form of scaling factors for the arm movements and/or left/right crossover mappings – i.e. the nonparetic real arm can be used to control movements of the paretic arm. The patient performs the task while simultaneously trying to imitate the actions he/she observes in the virtual arms. The control of the movements of the 'mirrored' arm can be gradually shifted from the intact arm to the paretic arm as the patient recovers, possibly accelerating further the speed of recovery.

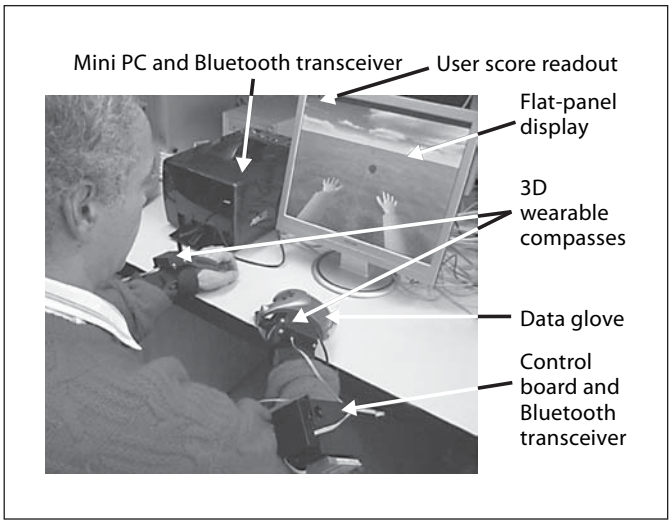

Fig. 4. VR-based cognitive therapy system.

Detailed position and event data from each game is recorded for analysis to both diagnose patient deficits and provide a record of improvement over training sessions.

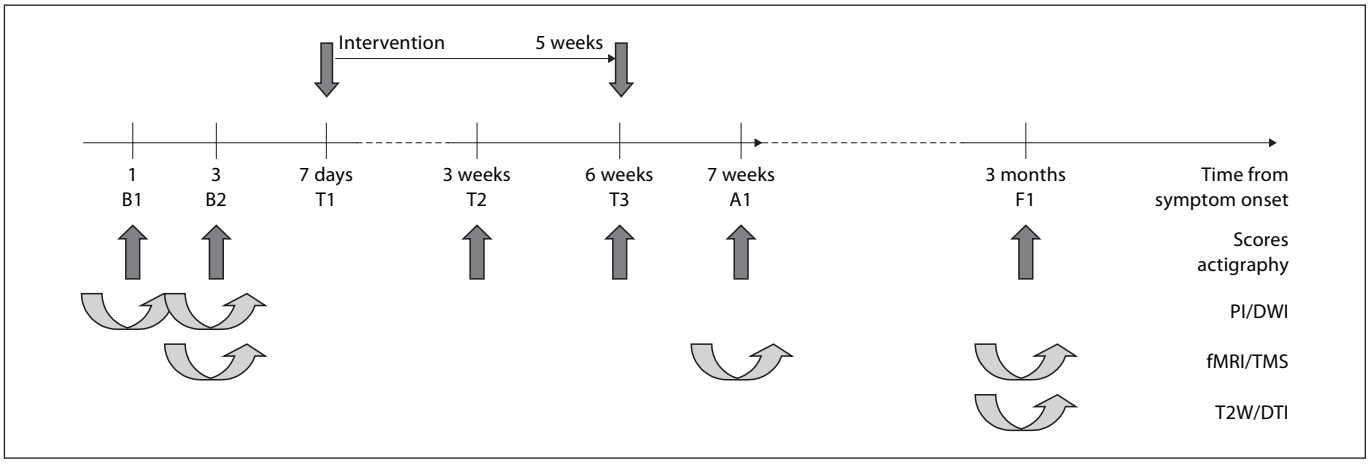

Fig. 5. Timeline of patient behavior evaluation. PI = Perfusion-weighted imaging; DWI = diffusion-weighted imaging; TMS = transcranial magnetic stimulation; DTI = diffusion tensor imaging.

Control Group

In the control group patients receive once daily basal task- and ADL-oriented physical therapy consisting of several modules such as vital (cardiopulmonary, etc.), static (posture, position, etc.), mobility (transfer, gait, etc.), and upper extremity functions. The rehabilitative effort available in the acute hospital (Neurology Department, University Hospital Zürich, USZ, Switzerland) is broadly similar to that in a rehabilitation hospital (Valens, Rheinfelden, Switzerland). The composition of the modules is the same in all participating clinics (vital: 0–5%, static: ~20%, mobility: 60–70%, upper extremity: 15–20%). One difference, however, is that the time basis in the Neurology Department averages 1.5 versus 2 h in the rehabilitation hospitals. Patients in the specific intervention groups receive daily basal task- and ADL-oriented physical therapy as described above. Additionally, concomitant therapies such as occupational therapy, logopedics, or neuropsychological therapies are offered to all patients depending on their individual needs.

Pilot Study – Treatment and Assessment Protocols

Treatment Protocol

The therapeutic interventions are carried out once a day on 5 days per week during a period of 5 weeks. Each treatment session lasts 45 min. During their stay in hospital, patients receive medical treatment, including recombinant tissue-plasminogen activator, whenever applicable. All patients receive standard physiotherapy.

Assessment Protocol

Patients who meet the entrance criteria are admitted into the trial during the first week after stroke onset. After initial clinical and functional assessment, patients are randomly allocated to either one of the experimental groups or to a control group. All procedures follow the ethical standards of the responsible institutional ethics committees. Informed consent is obtained from all patients participating in the study or from close relatives.

The timeline for patient treatment and evaluation is shown in figure 5. Clinical parameters are evaluated before (1st and 3rd day post-onset of stroke, baseline measurements B1, B2), midway (7th day, 3 and 6 weeks after stroke onset, referred to as T1, T2, T3), after the intervention period (7 weeks after stroke onset, referred to as A1), and during a follow-up, at 3 and/or 6 months after stroke onset (F1, F2).

Patient Selection

Inclusion Criteria

Stroke patients admitted to the emergency ward or stroke unit of the Neurology Department, USZ, are screened for inclusion. The diagnosis of stroke is based

on clinical history and examination and confirmed by MRI. The criteria for inclusion are: (1) diagnosis of acute ischemic brain damage in the first 48 h after symptom onset; (2) supratentorial localization of the stroke (comprising cortical as well as combined cortico-subcortical localization); (3) an obvious motor deficit of the hand with best hand function defined as Medical Research Council scale ≤3 (effort against gravity) lasting until the beginning of treatment; (4) older than 18 years of age; (5) alert and sufficient cooperation to permit full clinical examination, and (6) able to sit in a wheelchair or on a chair.

Exclusion Criteria

Patients older than 80 years of age, with a previous clinical history of stroke or a prestroke disability affecting the arm are excluded. Furthermore, pregnant women and patients with major cognitive deficits (comprehension deficits, severe depression, dementia, etc.), disturbances of basal sensibility, which may not allow testing of adequate electrical stimulation, epileptic seizures, progressive stroke, symptomatic intracerebral hemorrhage (ICH-associated increase of NIHSS >4 points), severe rheumatoid illnesses restricting joint mobility of the upper extremities, skin injuries, rash, burns, fresh scars, or inflammation on arms or hands, painful shoulder-hand syndrome, shoulder subluxation (palpatory >2 fingers), severe autonomic dysreflexia, i.e. requiring medication to treat autonomic dysreflexia, patients with metal implants, pacemakers or any other stimulation devices, prosthesis of bones or joints in the local region of treatment as well as patients with any severe medical diseases are also excluded.

Clinical (Descriptive) Assessment

At entry to the study, patient characteristics such as age, sex, side of paresis, site of lesion, type and onset of stroke as well as associated medical conditions are documented. On admission to the stroke unit at the Neurology Department, USZ (fig. 5, B1), the NIHSS [21] and the MMSE [22] are performed by clinicians involved in the routine treatment of the patients. The remaining acute neurological assessment (B1, B2) including neurological impairment – as measured by the Kunesch Score [23] – as well as a detailed sensory examination, handedness, and neuropsychological examination of each patient are performed prior to randomization. After the intervention period (A1), and during follow-up (F1), the overall outcome is assessed by the Modified Rankin Scale [24–26] in the Neurology Department of USZ.

Outcome Measures

Clinical Scales

The primary outcome is evaluated in terms of activity by means of the Chedoke Arm and Hand Activity Inventory [27]. Three secondary outcome measures are employed to follow the levels of activity (extended Barthel index [28, 29]) and participation (SF-36 [30, 31], Motor Activity Log [1, 32]). All measures meet the criteria of reliability and validity. They are assessed before randomization (B2), after referral to the rehabilitation clinic (Valens or Rheinfelden) after each treatment week and after the treatment period (A1, F1).

Behavioral Evaluation

In addition to clinical scores, we assess behavioral data to follow up the functional recovery process of the paretic upper extremity (fig. 5). In the acute stage (B2), by the end of every treatment week as well as after the treatment period (A1, F1), we also use a drawing test to follow recovery progress more closely [33]. Actigraphy recordings from the contra- and ipsilesional arm yield additional data about the amount of spontaneous motor activity on predefined days over the whole observation period [34].

Functional Brain Alterations

Neuroimaging

Functional Magnetic Resonance Imaging (fMRI). We use fMRI to study the evolution of activation patterns during the process of recovery. The dynamics of cerebral activation maps, especially their lateralization related to the course of motor recovery, showed changes during the course of motor recovery in several previous studies [35–37]. We therefore use the laterality index to quantify the amount of blood oxygenation level-dependent (BOLD) activation between the ipsi- and the contralesional hemisphere [38]. Furthermore, we compare the activation pattern of the patients in individual and group analysis with healthy subjects matched for gender, age and manual dexterity [39]. Before (B2) and after (A1, F1) intervention we measure BOLD fMRI to test the activation of motor areas for the different trained interventions. The patients have to generate with each hand isometric repetitive force pulses of 20% maximal voluntary contraction. In this

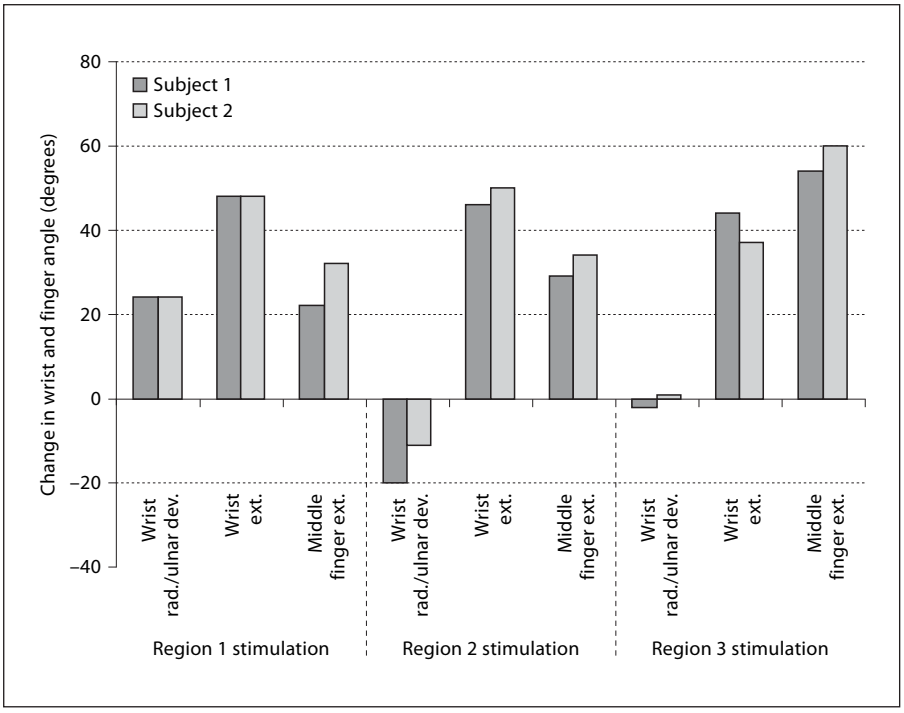

Fig. 6. Kinematic wrist and finger angular data for selective electrical stimulation of the wrist and finger extensors using three activation regions over the wrist and finger extensors. The results indicate that simultaneous activation of regions 1 and 2 produces co-contraction of radial/ulnar deviation and contraction of wrist extension with less activation of finger extension compared to the activation of region 3.

block design, including 21 s of force condition alternating with 21 s of rest (5 repetitions), the subjects are guided by color-coded feedback, where target and exerted forces are displayed on a screen in front of the subject.

Perfusion-Weighted Imaging, Diffusion-Weighted Imaging, Diffusion Tensor Imaging. In addition to fMRI, we use our regular clinical protocol comprising perfusion- and diffusion-weighted imaging. Lesion volumetry of perfusion- and diffusion-weighted imaging is based on automatic lesion outline at predefined thresholds relative to mean image intensity in the unaffected hemisphere [40, 41]. T_2 lesions are outlined manually by one of the authors.

Preliminary Results

The studies are still in progress and first results are appearing. Here, we summarize the results obtained to date for each of the three technologies being tested. Because only a few patients have been tested so far, between-subject power calculations have not yet been performed. For equivalent total amounts of training per patient, large numbers of subjects per test group ($n > 50$) may be required to achieve statistically significant results due to the high between-subject variability. However, we believe that because patient motivation to use the therapy technologies is high (as measured by user questionnaires), and patients receive our therapies in addition to normal therapy, much smaller numbers of subjects per group will be required to show improved outcomes. This testing scenario is realistic because our therapies are designed to supplement rather than replace existing therapy, with only minor increases in staff workload because of the semiautomated nature of the therapy systems. The main results we expect for each of the three technologies are improved functional recovery as measured by the ADL tests, and cortical activations that are more normal than in the control cases.

Functional Electrical Stimulation

Subjects after stroke with remaining upper limb deficits often suffer from abnormal flexion hyperactivity in shoulders, elbows and arms. It could be shown that FES can overcome these abnormal synergies in the elbow by stimulating the triceps muscle during reaching activities [19]. For achieving functional use of the hand it is also necessary to be able to overcome similarly occurring abnormal hyperactivity in the fingers.

Preliminary tests were performed in 2 stroke subjects with abnormal movement patterns to selectively acti-

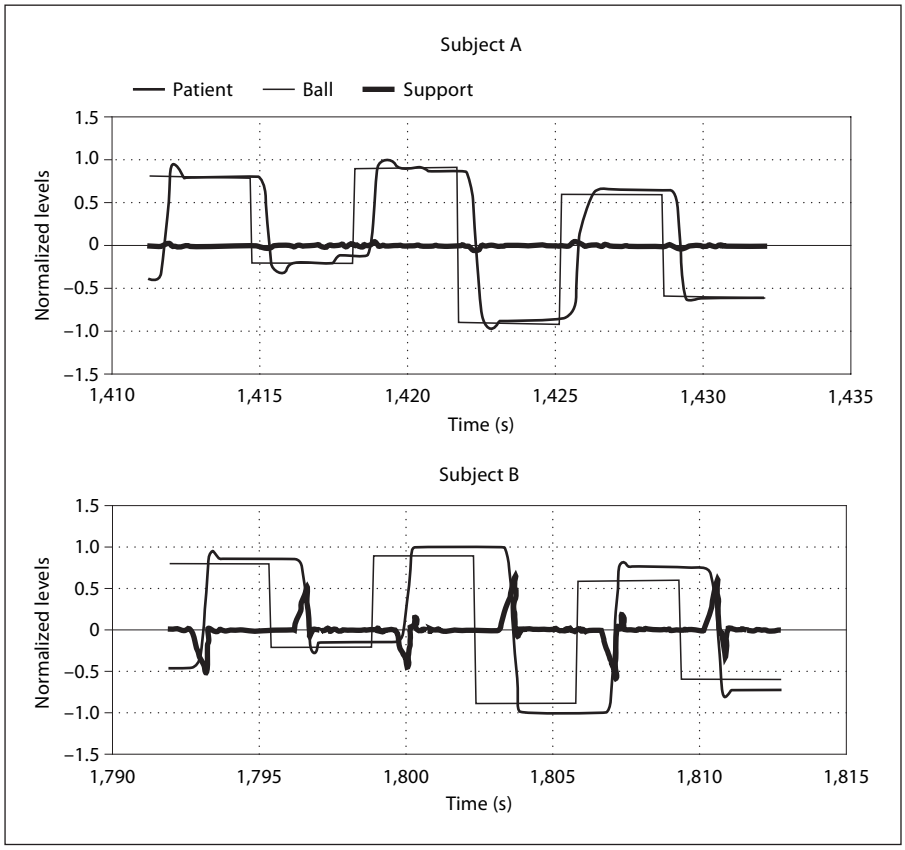

Fig. 7. Movement and force support recorded from 2 hemiplegic subjects playing the ball game.

vate wrist and finger muscles. Both subjects (female) had severe paresis of their right arm and hand, which resulted in a Fugl-Meyer score of 20/66 and 27/66. For selective activation of wrist and finger extensors by means of transcutaneous electrical stimulation three regions were found over the finger and wrist extensor muscles that resulted in differential wrist and finger movements. The goal was to activate finger extensor muscles with minimal ulnar and radial deviation in the wrist and to activate wrist extension with minimal activation of the finger extensors. This second strategy would allow stroke subjects to close their hands without compromising a natural wrist position achieved by stimulating the wrist extensors. Region 1 activated wrist extension combined with wrist radial deviation and some finger extension. Region 2 activated wrist extension combined with wrist ulnar deviation and some finger extension. Region 3 mainly activated the finger extensors with almost no ulnar/radial deviation and some wrist extension. In both subjects, activation regions could be found at moderate levels of stimulation (150 μs pulse width, 25 Hz stimulation frequency and amplitudes of 18–22 mA). To illustrate the results (fig. 6) the angular change of wrist and finger positions during selective stimulation of the three regions was measured with a P5 data glove (Essential Reality Inc.). All three regions were stimulated in consecutive order, first region 1, then region 2, and finally region 3. Each region was stimulated with the following pattern: 1 s amplitude ramp up, 5 s constant stimulation at moderate amplitude of 18–22 mA, 1 s amplitude ramp down with 1-second resting periods between patterns. Resting position before stimulation was 0° radial/ulnar deviation, 40° wrist flexion and 80° finger flexion. Stimulation of region 3 (for finger extension) showed almost no radial/ulnar deviation and more finger extension than stimulation of regions 1 and 2. Stimulation of region 1 resulted in wrist radial deviation and more index finger activation than ring finger activation. Conversely, stimulation of region 2 showed more ring finger activation than index finger activation. Both regions 1 and 2 produced more wrist extension than region 3. On the other hand, finger extension, especially for the middle finger, was partially reduced compared to stimulation of re-

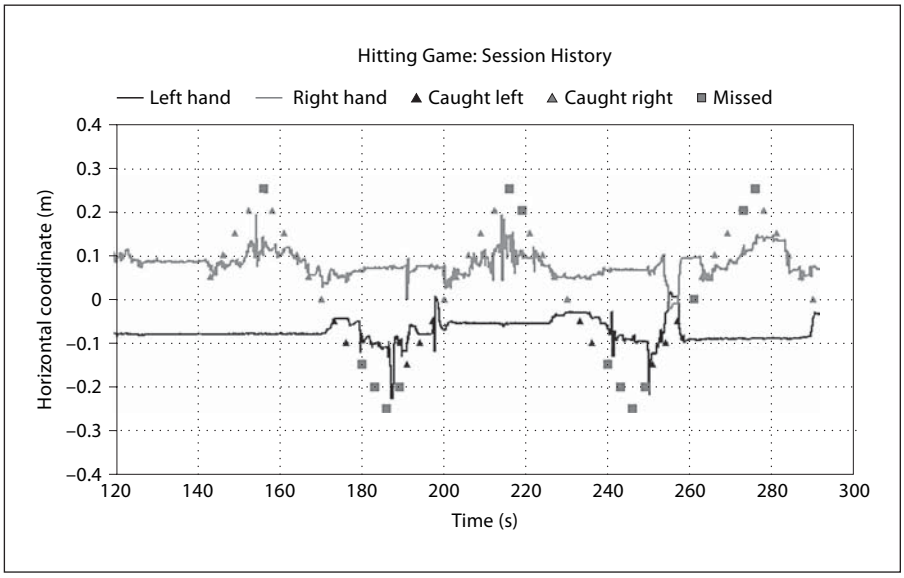

Fig. 8. Sample session history from patient 1, usability and assessment pilot.

gion 3. These results show that finger extension can be functionally stimulated to overcome paresis and flexion hyperactivity in the hands of subjects after stroke. In addition, the results indicate that a certain level of selectivity in wrist and finger extensor activation can be achieved with transcutaneous electrical stimulation.

ARMin

A pilot study with 10 healthy subjects and 5 chronic stroke patients was carried out to analyze comfort, functionality, acceptance, and whether the patients are able to perform the proposed tasks. With the 5 patients a series of sessions were performed, each including 30 min of movement therapy and 30 min of game therapy. The 5 patients used the robot for more than 30 h altogether.

The fixation of a patient in the robot takes approximately 5 min. The robot can easily accommodate subjects with body sizes between 155 and 192 cm. The robot allowed reliable trajectory recording and repetition with adjustable velocities during movement therapy. During game therapy it provided interactive support for the patient. Participants and therapists gave ARMin high grades with respect to comfort, design, and clinical usability. Although it was not the primary goal to study the therapeutic effect during the relatively short training sessions, an improvement of the patients' motor functions could be observed. From session to session the robot support decreased, while speed and range of motion increased and joint coordination improved. Thus, the patients could play games with increasing difficulty levels.

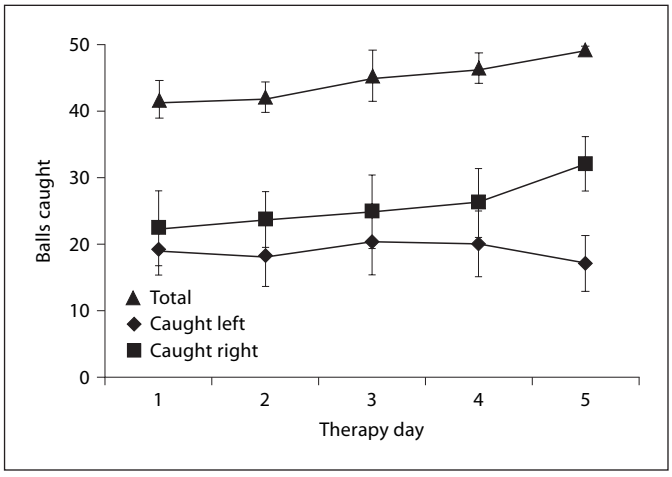

Fig. 9. VR game performance over successive therapy days for stroke patient 2 of the usability and assessment pilot starting on the 7th day after symptom onset. Each therapy session consisted of six sets of 50 balls each. Error bar = ±1 standard deviation.

Figure 7 shows the results of a game therapy performed with 2 chronic hemiplegic subjects. The subjects had to catch a visually displayed ball (fig. 3) by moving their hand towards the ball. Subject A was able to catch all balls without any robotic support, whereas subject B needed

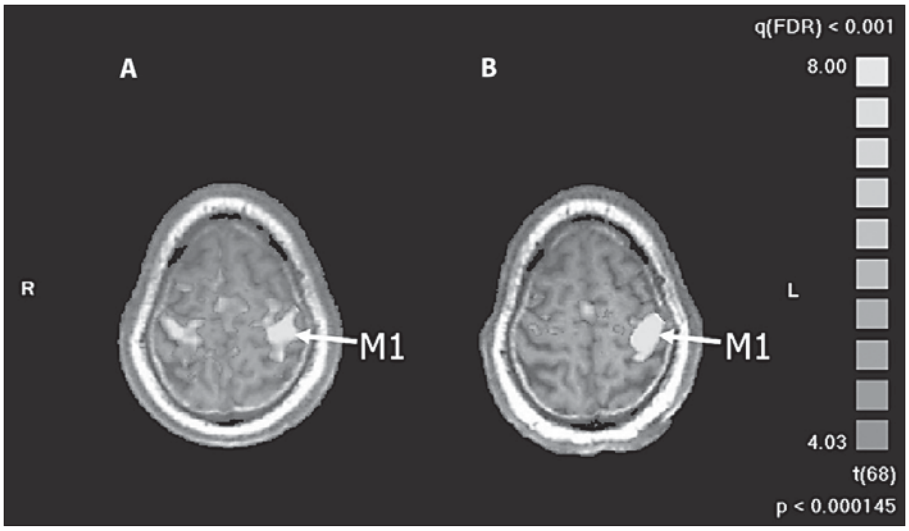

Fig. 10. Changes in cortical activation as a function of intervention: involvement of M1 during dynamic force generation with the paretic right hand. **A** Bilateral activation in the primary motor cortex (M1) before intervention. **B** Contralateral activation in M1 3 months after intervention.

some support to catch the balls. ARMin allows measuring the voluntary force of the subjects and storing it for later therapy assessment.

VR Cognitive Therapy

The VR cognitive therapy system was implemented using the hitting scenario in pilot studies on the following groups of subjects: (1) healthy subjects, mean age 29 ± 4 years (n = 19, mean standard ± deviation), usability pilot study; (2) stroke patient, age 63 (n = 1), usability pilot study, and (3) stroke patients, ages 62 and 56 (n = 2), usability and assessment pilot studies.

Both the healthy subjects and the stroke patients were able to use the system for learning how to perform the task within a short time after the commencement of the first test session. For the initial settings given (1 ball every 2.5 s, ball start location random or wave pattern), most healthy subjects and patients were able to intercept between 70 and 100% of the balls. User acceptance of the system was high (anecdotal and questionnaire responses); in particular the patients tested expressed a desire to use the system on an ongoing basis.

Figure 8 shows a plot of the data for a test run with one of the stroke patients, showing the movements of the left and right hands as well as the fates of each of the balls (caught with left hand, caught with right hand, or missed). In this example the balls appeared every 2.5 s in a wave pattern. It can be seen that most of the 'missed' events occurred towards the extremities of movement, and that a greater proportion of balls were missed on the left side than the right side. The patient's paretic side was the left side and the patient was right-handed when healthy, so the relative contribution of paresis and handedness to the left/right performance imbalance can only be assessed after further testing as the patient regains left arm function.

Figure 9 shows the performance of patient 2 from the usability and assessment pilot studies over successive therapy days. Each therapy session consisted of six sets of 50 balls each. The mean score on the last day was significantly higher than that on the first day (t test, $p < 0.01$). As the patient had reached virtually perfect performance by the fifth day, continued therapy would probably have benefited from an increase in game difficulty (increased ball speed, increased dispersion of balls, etc.).

Figure 10 shows the change in cortical activation in a patient who underwent VR cognitive therapy for 2 weeks. The patient was instructed to perform a right-handed grip strength task in the MRI scanner. The bilateral activation of M1 that was present shortly after the stroke changed significantly towards normal localized contralateral activation. The generalizability of this result, and the extent to which VR cognitive therapy contributed to this result, will be determined in future control tests with patients undergoing normal physiotherapy.

Conclusions and Outlook

Our interdisciplinary approach to the application of multiple technologies in a simultaneous study of their efficacy for stroke rehabilitation permitted a well-validated, consistent evaluation of each of our three complementary approaches to neurorehabilitation. This synchronized assessment of multiple new technologies in an extensive simultaneous clinical study is, to the best of our knowledge, a novelty in the field of neurorehabilitation. While some of our initial results from patient testing are promising, more data is required before we can make definitive statements concerning the efficacy of our different methods. The question of whether a combination of our new technologies is more effective than any single method alone is open, and should be the subject of a future study.

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