

Results of rehabilitation outcome in patients and protocol for future clinical trial

Deliverable D4.5

List of Partners:	ETH Zurich, CH Hocoma AG, Volketswil, CH University of Ljubljana, SI Universitat de Barcelona, ES Neurological Clinic Bad Aibling, DE	(ETH Zurich) (HOCOMA) (UL) (UB) (NKBA)
Document Identifier:	MIMICS-D4.5-pu.pdf	
Version:	3.0	
Due Date:	2010-12-23	
Organisation:	NKBA	
Deliverable:	4.5	
Milestone:	4.4	
Work Package:	4	
Task:	4.2 and 4.3	
Dissemination:	public	
Authors:	Friedemann Müller, Jeannine Bergmann, Alexander König, Domen Novak, Matjaž Mihelj, Marko Munih, Jason Kastanis, Lukas Zimmerli	
Approved by:	Marko Munih, Lars Lünenburger	

Table of Contents

1	Summary	3
2	Lokomat	4
2.1	Technological setup for clinical investigations	4
2.1.1	Scenario.....	4
2.1.2	Multi-sensorial data processing (as described in Deliverable 3.2).....	7
2.2	Clinical evaluation	7
2.2.1	Controlling activity.....	9
2.2.2	Controlling psychophysiological states	12
2.2.3	Motivation	13
2.2.4	Rehabilitation outcome	16
3	HapticMaster and Armeo	18
3.1	HapticMaster and Armeo platform	18
3.1.1	Scenarios.....	18
3.2	Clinical evaluation	20
3.2.1	Subacute stroke patients' psychophysiological responses to rehabilitation	21
3.2.2	Chronic stroke patients' psychophysiological responses to rehabilitation	24
3.2.3	Stroke patients' biomechanical responses to rehabilitation	26
3.2.4	Patient motivation in the River scenario with two rehabilitation platforms	28
3.2.5	Effects of type of virtual scenario on patient motivation.....	31
3.2.6	Adaptive discriminant analysis: open-loop and closed-loop control	32
3.2.7	Evaluation of the River scenario	37
3.2.8	Study on Fitt's law using Armeo	37
4	Future clinical trial	40
4.1.1	Future collaboration with UB.....	40
4.1.2	Future extension of ongoing clinical trials.....	40
5	Conclusion and Outlook	42
6	References	44

1 Summary

The goal of the MIMICS project is to enhance existing robot-assisted rehabilitation methods with multi-sensorial acquisitions, multimodal displays and technical cognition. The Lokomat is the main component of the robotic system for the lower extremity and the HapticMaster and Armeo for the upper extremity.

The next two sections give a specific overview of the experimental evaluations of the systems and applications.

Section 2 details the lower extremity (Lokomat). Section 3 describes the upper extremity systems (HapticMaster and Armeo). Finally in section 4 we present conclusions on the future work out of the MIMICS project.

2 Lokomat

2.1 Technological setup for clinical investigations

2.1.1 Scenario

Scenarios for the Lokomat must **make sure the patient participates actively** in the walking movement while keeping the patient as **motivated and engaged** as possible. Four scenarios of increasing complexity were designed and tested with patients.

2.1.1.1 Scenario for control of physical effort (“Dog scenario”)

To control physical effort to a desired level, we provided patients with information on their current physical effort via graphical feedback. The position of a white or red dot in comparison to a reference coded the current deviation of the desired from the actual physical effort. By increasing or decreasing physical effort, the patient could move the white dot and match the desired to the actual physical effort by closing the control loop via the visual system. To make the virtual environment enjoyable and easy to understand for the patients, the reference of the desired physical effort was displayed as a dog walking on in a forest.



Figure 1: Virtual scenario used for control of physical effort

2.1.1.2 Scenario for control of psychophysiological states

In order to influence the psychophysiological state of subjects, we programmed a **collect and avoid scenario** where subjects have only one degree of freedom in the virtual environment (Figure 2, as described in deliverable 2.2.). While we had initially proposed a “city scenario”, where patients could steer an avatar through a virtual world, we replaced this “city scenario” by a “forest scenario”, which did not allow left and right movements. All actions took place in the main axis and changes in walking

direction were not possible in order to accommodate even subjects with severe lesions. Instead, the patients were able to **influence their walking speed by increasing or decreasing their participation activity**. Some objects (coins) had to be collected while others had to be avoided (stones). The closest object disappeared after a predefined time period. It could be collected (coins) by approaching it at increased walking speed, i.e. higher activity. It could also be avoided (stones) by decreasing walking speed, i.e. lower activity, such that the object would have disappeared before the patient would reach it. To support potentially impaired visual capabilities of the subjects, the next object on the walking path was marked with blinking arrows. In addition, we introduced questions with varying difficulty which had to be answered by the subjects.

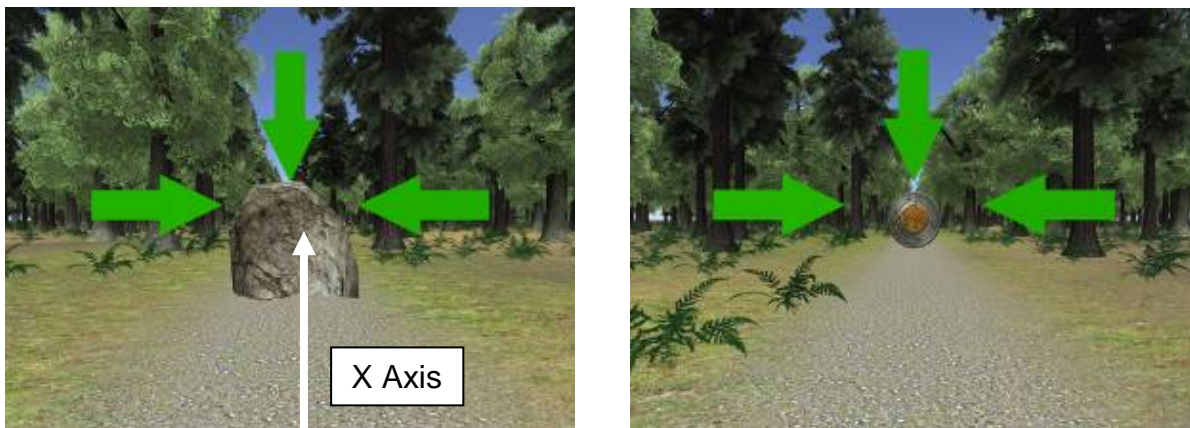


Figure 2 The improved virtual task applied to patients with more severe lesions. All movements happen on the main axis (x axis). Stones (left) have to be avoided, while coins (right) have to be collected. The green arrows indicate objects of interest for better recognition of severely affected subjects.

2.1.1.3 Proxemics scenario

The goal of this research is to assess whether **reinforcement learning (RL)** can be used to create a situation where a virtual character is able to affect the behaviour of participants. In other words the virtual character learns which of its behaviours result in the desired behaviour of the participant. The behavior to be generated in the participant was based on the concept of proxemics. [Hall 1966]. Proxemics deals with the issues of interpersonal distances. Taking advantage of this theory, the goal was to get the participant to move 30 meters backwards. The participant could move in the virtual world by adapting his or her posture. Leaning forwards generated a forward motion in the virtual environment and vice versa. The goal of moving the participant to the pre-determined position was achieved indirectly by using RL to control the actions (Figure 3) of a virtual character. RL controlled whether the virtual character moved forwards or backwards, idled or waved at the participant. The validity of this approach was investigated in an experiment with 30 healthy volunteers performed at UB [Kastanis and Slater 2010].



Figure 3: The scenario is an alleyway that contains an avatar seen from the participant's viewpoint: a) the character is quite far away, b) he has walked closer c) calls to the participant to 'come here!' while waving, d) has approached closer, e) is within personal distance.

2.1.1.4 City navigation scenario

Based on previous experience in the MIMICS project UB has developed a scenario, where the patient is navigated through a virtual city. The patient can control his or her speed by putting effort and actively moving his legs while in the Lokomat device. **To motivate the patient to actively participate, various virtual characters (avatars) are placed in the city environment.** The characters can perform various actions such as telling the patients to go slower/faster or maintain their speed. These actions can be performed with or without the avatar being aware of the patient. Awareness can be displayed by having the avatar follow the patient with his gaze. From a previous experiment (2.1.1.3) where UB examined the application of RL, it was found that for avatars to be effective in interaction, the human participant needs to be engaged in this, otherwise the actions of the avatar are irrelevant to the human. One of the factors that appeared to be important in engaging interaction was the ability of the avatar to look at the eyes of the participant. This issue is essential in the design of applications that interact with the user and it is what this experiment will be

investigating. As previously the choice of actions is performed automatically by an **RL agent** aiming to maximize patient motivation. The goal of this study is to examine whether the effect of patient awareness, as implemented with avatar gaze control in this case, has on motivation and active participation.



Figure 4 Views of the virtual city environment

2.1.2 Multi-sensorial data processing (as described in Deliverable 3.2)

2.1.2.1 Control of physical effort

Physical effort was defined in two ways, by a physiological marker and one non-physiological marker. As physiological marker, we used heart rate which was shown to increase with increasing physical stress (Thomas et al. 2007). As non-physiological marker, we chose a **weighted sum of interaction torques (WIT)**, which represents the interaction torques between patient and Lokomat weighted such that they reflect therapeutically desired activity (Banz et al. 2008).

Heart rate as well as WIT were computed in real time. Heart rate was extracted from Electrocardiogram (ECG) using an RR beat-to-beat detection algorithm as described in Deliverable 3.2 and in (Malik 1996). Control was then performed by mapping the error between desired and actual physical effort via a P gain into a visual stimulus.

2.1.2.2 Control of psychophysiological states

The final control system for the patient's psychophysiological state was implemented with the Kalman Adaptive Linear Discriminant Analysis (KALDA) System. Details on the KALDA can be found in Deliverable 3.2. Signals used were the Electrocardiogram (ECG), skin temperature, skin conductance and breathing frequency.

2.2 Clinical evaluation

Table 1 lists all the studies conducted at ETH and NKBA as part of MIMICS, in chronological order. For each study, it lists the question that we wished to answer with the study, whether it was reported in a previous deliverable, and whether it was a clinical study. Only clinical studies are described in this deliverable.

Question we wished to answer	Clinical study?	Reported in previous deliverables	In this deliverable
1. Can we record psychophysiological signals with our equipment?	no	D3.1	no
2. What is the influence of standard Lokomat training on psychophysiological signals	no	D4.2	no
3. Do passive stimuli that elicit negative or positive emotions evoke psychophysiological responses that can be recorded?	no	D4.2	no
4. Is it possible to elicit different psychological states via a virtual environment and differentiate them by investigation of physiological recordings?	yes	D4.3	no
5. How do medication and concomitant disease influence heart rate?	yes	no	2.2.1
6. Is it possible to control patient participation via virtual environments or adaptation of treadmill speed?	yes	D6.2(2010 – partially)	2.2.1
7. Is it possible to control cognitive load to a desired level by adaptation of task difficulty?	yes	no	2.2.2
8. How do the scenarios affect patient’s motivation?	yes	D6.2(2010 - partially)	2.2.3
9. What is the activity in the paretic and non-paretic leg while performing the “dog scenario”?	yes	D6.2(2010 - partially)	2.2.1
10. Can the activity in the paretic leg be improved using a paretic leg control mode?	yes	D6.2(2010 - briefly)	2.2.1
11. What is the course of the intrinsic motivation during a 4-week Lokomat training with and without VR?	yes	no	2.2.3
12. Does VR-enriched Lokomat therapy improve the rehabilitation process and outcome?	yes	no	2.2.4

Table 1: Lower extremity studies conducted at ETH Zurich and NKBA

The results of initial experiments performed with healthy subjects at ETH that are reported in other deliverables are briefly reviewed. The deliverables, in which these results are reported are summarised in Table 1. We investigated the usability of our equipment in combination with the Lokomat (Table 1, experiment 1) to identify possible artefacts induced by the Lokomat robot. We found that the **skin conductance signal** was susceptible to noise, which however could be filtered out by a bandpass filter. Second, we investigated the effects that **different gait speeds, levels of guidance force or body weight support** had on subjects in the Lokomat (Table 1, experiment 2). We found that breathing frequency and heart rate increased with increasing physical effort induced by higher gait speeds, lower guidance forces or lower body weight support. In a third experiment, we investigated the effects of passive stimuli designed to elicit **positive or negative emotions** in subjects (Table 1, experiment 3). Questionnaires confirmed that the stimuli did have the desired emotional effect on subjects; psychophysiological recordings however failed to reflect these changes in emotions in a statistically significant way. Therefore, experiment 4 (Table 1) involved a collect and avoid task for healthy subjects at ETH Zurich and patients at NKBA. Significantly different results were found. These are summarized in Deliverable 4.5 and are published in (Koenig et al. 2010b).

2.2.1 Controlling activity

The initial study on control of patient participation was performed at ETH Zurich before transfer to the clinical partner NKBA. Exemplarily, two patients under the influence of **beta blocking medicine** were recorded using the “dog scenario” in section 2.1.1.1. In both cases, **control of heart rate was not possible**, even in the presence of high physical effort. As this confirmed the expectations of the influence of beta blockers, use of these agents were added as exclusion criterion for experiments in which heart rate was controlled.

To control the patient’s active participation during VR-enriched Lokomat training two studies were performed at ETH Zurich and NKBA using the “dog scenario” described in 2.1.1.1. The goal of the first study was to investigate approaches to controlling active participation in patients during robot-assisted gait therapy. Results are submitted for publication in the Journal of Neural Engineering and Rehabilitation (Koenig et al. 2010a).

The aim of the second study was to compare the **activity in the paretic and non-paretic leg and to improve the activity in the paretic leg**. We chose a weighted sum of interaction torques (**WIT**) to measure physical effort. The measurement included 5 conditions, which were defined over different desired WIT (maximal WIT, 30%, 60% of maximal WIT, maximal WIT and minimal WIT).

A total of 11 stroke patients participated in the study. Results are in preparation for publication. In the following section we present data of a representative patient.

We designed two experiments. In the first experiment WIT values were calculated using the interaction torques from all 4 joints (hip and knee joint of both legs), i.e. a **bilateral control** of the VR (Figure 5).

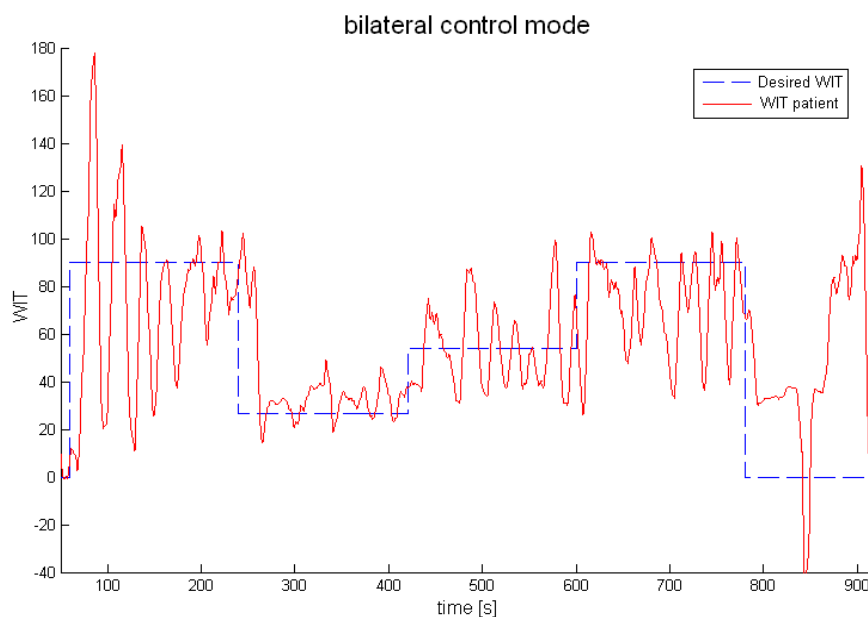


Figure 5 Desired activity profile and WIT values of a patient using the bilateral control mode.

While condition 2 and 3 (30% and 60% of maximal WIT) could be tracked well, the patient had problems in reaching the maximal desired WIT towards the end of the experiment.

In the second experiment only a **unilateral control** across the hip and knee joint of the paretic side was used to calculate the WIT and regulate the avatar (Figure 6).

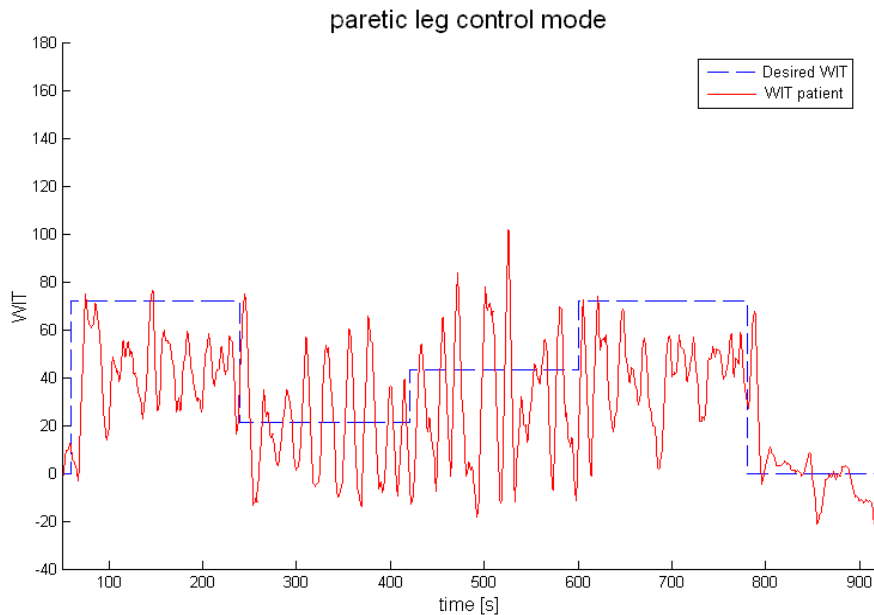


Figure 6 Desired activity profile and WIT values of the patient using the unilateral control mode.

WIT of the first and second experiment were standardized on baseline to compare the bilateral and paretic control mode (Figure 7). **The patient showed increased WIT values in the paretic leg while using the VR application in both control modes** compared to the baseline in which the patient walked in the Lokomat without any instructions. In conclusion, the patient was able to modulate the activity in his paretic leg and the application was an appropriate strategy to enhance patient's participation.

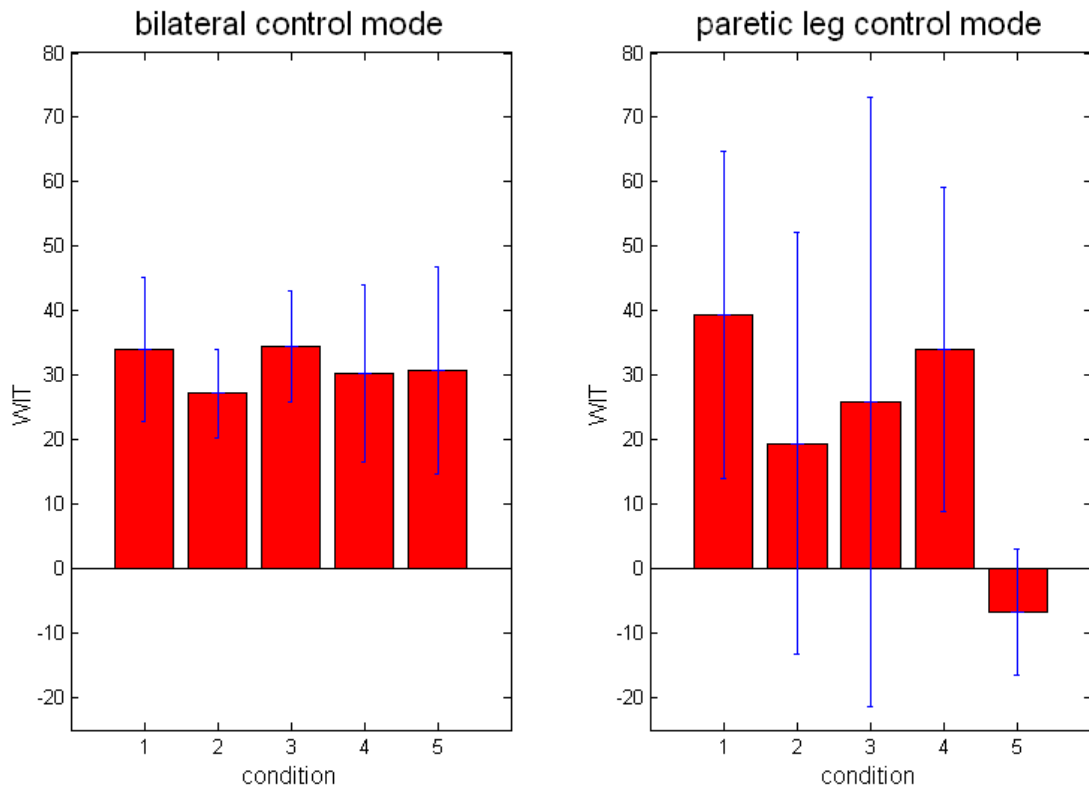


Figure 7 WIT values and standard deviation in the paretic leg standardized on baseline in the five conditions using the bilateral and unilateral control mode.

As shown in figure 7, WIT values measured in the paretic leg were increased in the conditions with maximally desired WIT (condition 1 and 4) using the paretic leg control mode compared to the bilateral control mode. Condition 2 and 3 in the paretic leg control mode were modulated by the desired WIT profile of 30% and 60% of the maximal WIT. The paretic leg control mode animated to a differentiated activation in the paretic leg.

To quantify each joint's contribution in the 5 conditions, we calculated the WIT differences in the hip and knee joint between condition 1 and 2, 3 and 2, 4 and 3 and 4 and 5 (Figure 8).

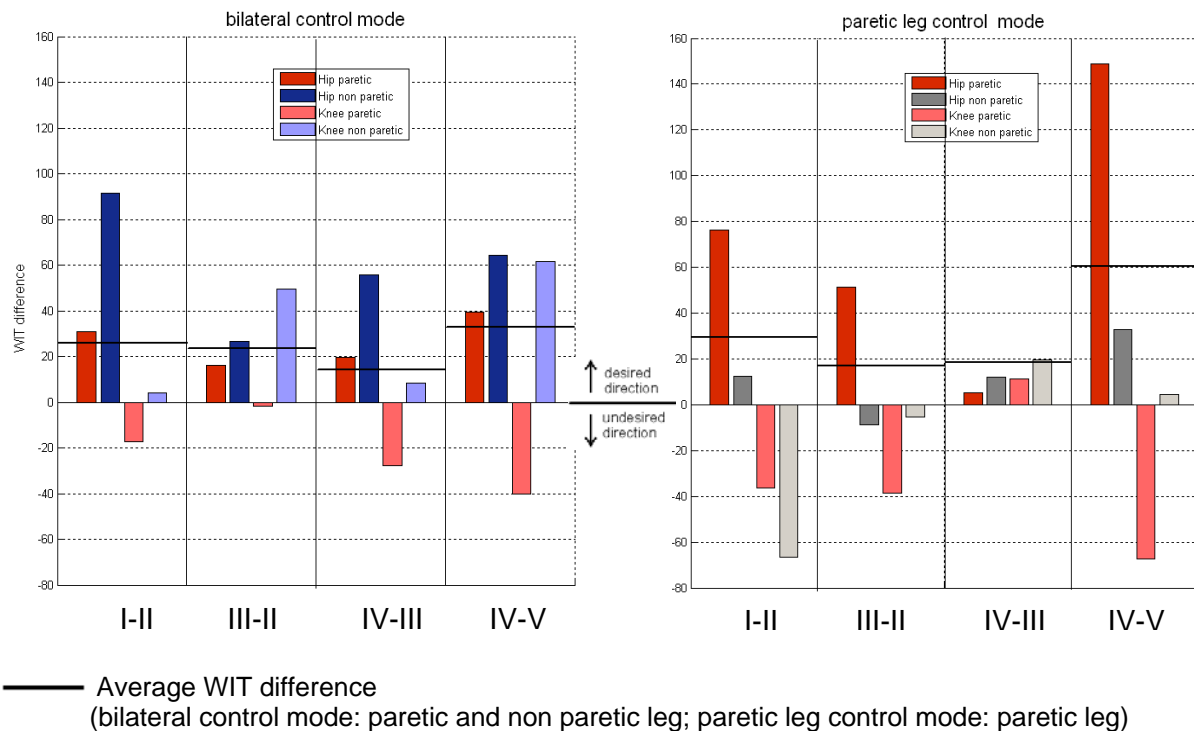


Figure 8 WIT differences between the five conditions for the hip and knee joint in the parietic and non parietic leg.

In the **bilateral control mode** the activity profile was modulated **mainly by the non-parietic leg**. However the **parietic hip acted** in a desired manner and assisted essentially the non-parietic leg. The parietic knee was passive or even performed an undesirable movement. In the parietic leg control mode the parietic hip was the main regulator of the five conditions while the parietic knee was acting counterproductively. In summary it was possible to **induce a considerable therapeutically desired effort on the parietic hip joint** whereas the parietic knee joint couldn't be used as efficiently.

2.2.2 Controlling psychophysiological states

Control of psychophysiological states was performed at ETH in five exemplary stroke patients using physiological signals, task success data from the virtual environments and force data from the Lokomat. We **controlled the cognitive load** of patients to a desired level, where subjects were neither under-challenged and bored nor over-challenged and stressed. Results were verified by asking the Self-Assessment Manekin Questionnaire (SAM) (Bradley et al. 1994).

We performed an online estimation of the current cognitive load and adapted the virtual environment such that that task described in 2.1.1.2 became easier if the subjects were overchallenged and harder if the subjects were bored. To evaluate how well our online estimation algorithm worked, we asked subjects about their current cognitive load at each time point the algorithm had estimated cognitive load. In addition, the experimenter rated the current cognitive load. The questionnaire

answer had no influence on the closed loop control of physical effort. We then computed the percent match between the questionnaire answers and the estimator. **The classifier could predict the cognitive load of healthy subjects with $85\pm 10\%$, and the one of patients with $80\pm 8\%$.** These numbers however refer to the percent match between the experimenter and the classifier. While the match subject vs. classifier was similar for healthy subjects, it was lower in **patients being $53\pm 33\%$.** This might be caused by limited self-assessment capabilities of the patients. These results are submitted to the journal "Transactions on Neural Systems and Rehabilitation Engineering" (Koenig et al. 2010c)

In conclusion, psychophysiological measurements are a useful tool to assess the cognitive load of subjects during robot-assisted gait training. For clinical applicability, the sensors must be improved such that they can be attached in a faster and more reliable fashion. Heart rate, for example, should be recorded with a belt worn around the chest rather than using wet electrodes to reduce setup time for the recording and improve clinical applicability.

2.2.3 Motivation

For assessment of the patient's motivation subjects completed the **Intrinsic Motivation Inventory (IMI)** [McAuley et al. 1989 & McAuley et al. 1991] after performing the "dog" and "city scenario" on the Lokomat and a Lokomat training without VR. Overall we found high IMI-scores for the measured scales 'interest/enjoyment', 'value/usefulness', 'effort/importance', and 'perceived competence' as well as low scores in the reverse scoring scale 'pressure/tension'. Therefore subjects participating in the study are **generally highly motivated** and interested in the therapy with the Lokomat. The 'interest/enjoyment' scale is considered the self-report measure of intrinsic motivation and showed significant differences between the scenarios and a significant difference between the city scenario and the dog scenario and between the city scenario and Lokomat without VR to the disadvantage of the city scenario.

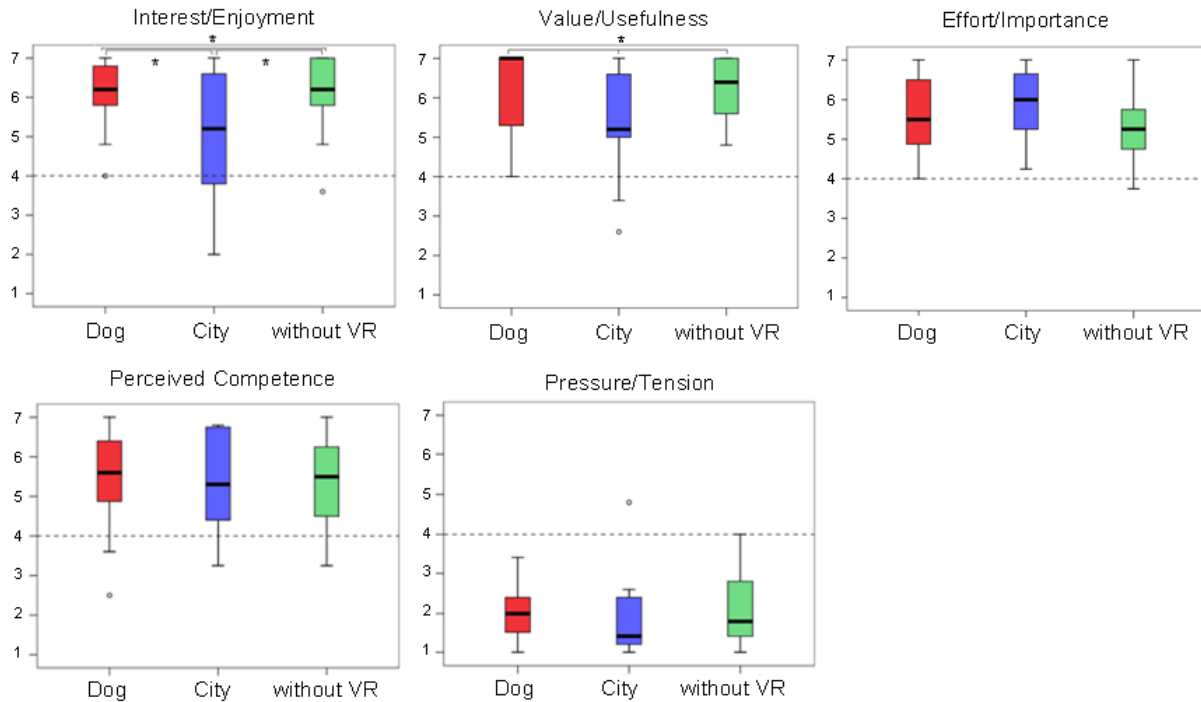


Figure 9 IMI scales after performing the dog scenario [N=24], the city scenario [N=9] and a Lokomat training without VR [N=17]; 1=not at all true, 7=very true; * = $P < .05$.

The results prove that the one-dimensional dog scenario is more motivating for patients with hemiplegia than the city scenarios with changes in the walking direction (see 2.1.1.2). This is in concordance with observations in the therapeutic sessions, that showed considerable difficulty in hemiplegic patients to control reliably directional movements. An explanation for the high IMI-scores after the Lokomat training without VR could be that the questionnaire was assessed after the first training on the Lokomat, when patients were fascinated and pleased about the new device, since getting back to walking is the ultimate goal in that stage of rehabilitation. To verify that speculation we aimed to assess the questionnaire over a longer therapy period.

In a **clinical study** we applied the IMI at the beginning, in the middle and at the end of a **4 week Lokomat therapy block** (total of 12 Lokomat sessions). First observations indicate a decrease of intrinsic motivation (scale, interest/enjoyment') in patients performing conventional Lokomat therapy over 4 weeks, while patients using MIMICS-VR even improved their motivation (Figure 10). Because some patients are limited in their self-assessment capabilities we rephrased the questionnaire in the manner the therapist was evaluating patient's motivation.

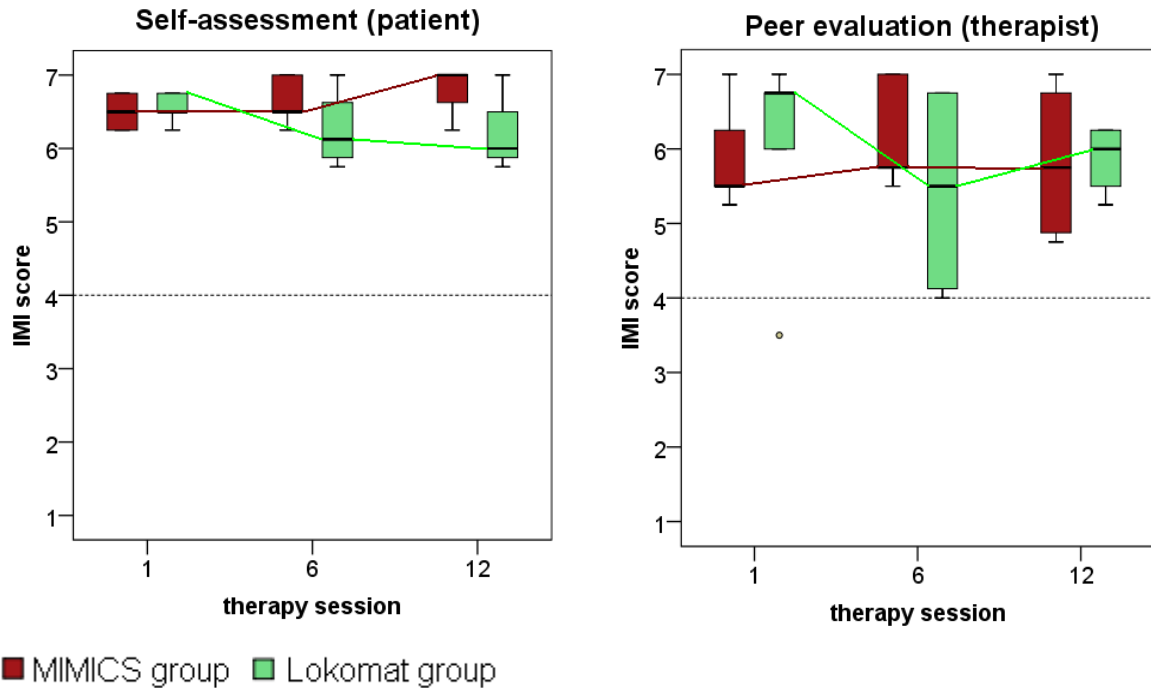


Figure 10 IMI scale, interest/enjoyment' as self-assessment and peer evaluation during a 4 week Lokomat therapy with [N=4] and without [N=4] VR. IMI was assessed after the first, the 6th and the 12th therapy session.

Additionally we did a crossover at the end of the study, where subjects from the MIMICS group (VR) had a Lokomat session without VR and subjects of the Lokomat group (without VR) received a therapy using MIMICS-VR for four weeks. First results indicate **higher intrinsic motivation** in both groups performing **VR-enriched Lokomat therapy** compared to standard Lokomat (Figure 11). Interestingly both groups rate the standard Lokomat training as more valuable and useful than the training with VR.

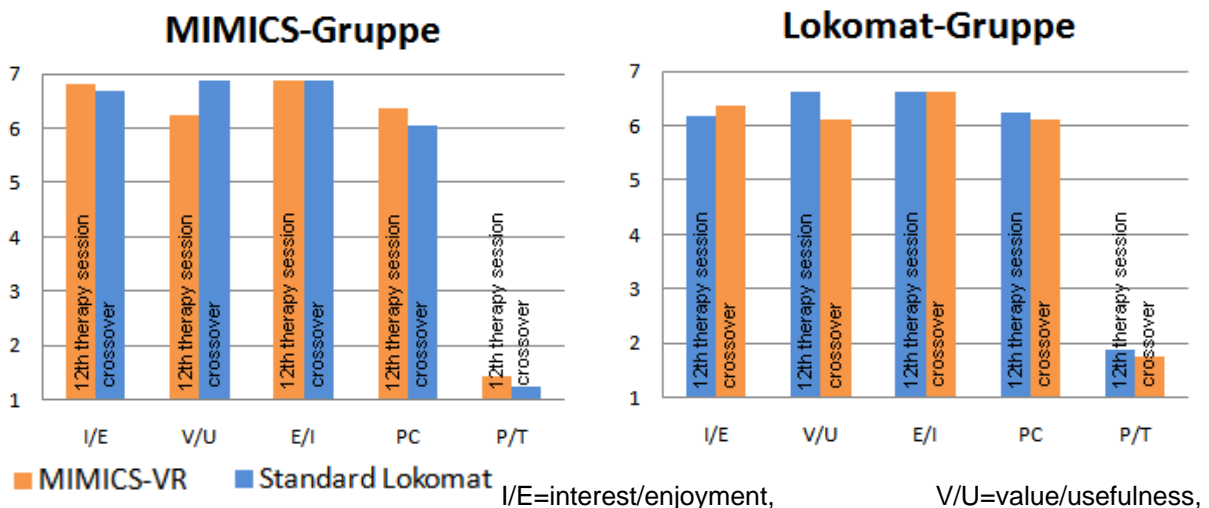


Figure 11 IMI scales of the MIMICS group [N=4] and the Lokomat group [N=4] after the 12th and the crossover Lokomat session.

In an additional interview 11 of 13 patients answered that they preferred the VR-enriched Lokomat compared to the training without VR, that VR was therapeutically more worthwhile and less boring. 4 were confused by VR. 12 were more motivated while the Lokomat training with MIMICS-VR and 9 of the 13 patients preferred the VR-enriched therapy to the Lokomat therapy without VR.

The feedback of the therapists working with VR was generally positive. They reported high motivation and effort of the patients, improvements in patients' endurance and attention and encouragement to focus on the screen (instead of the feet or the floor) what involved additionally the secondary effect that patients had to straighten up.

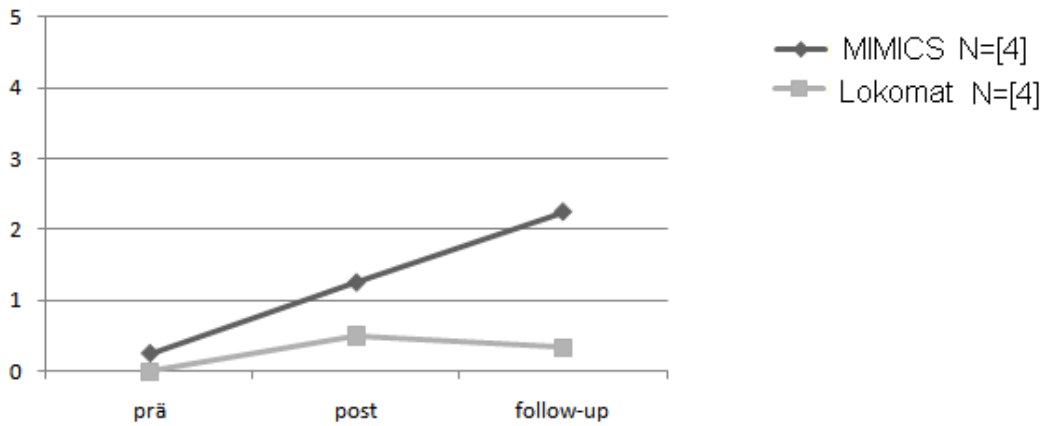
2.2.4 Rehabilitation outcome

The final aim of MIMICS is to enhance patient's motivation and participation in therapy and thus to improve the rehabilitation process and outcome. To examine this hypothesis on the basis of the technology developed a pilot study has been designed at NKBA as planned in the description of work. 10 patients with stroke underwent a 4 week gait training (3 sessions per week). 5 subjects received VR-enriched Lokomat therapy and 5 patients received standard Lokomat training without VR. The objective of the controlled and randomized clinical study was to determine changes in several walking-related outcomes due to VR-enriched robot aided gait therapy. Patients were in the subacute stage and severely disabled as is the case in most patients after a significant stroke. In those patients more effective therapy is most appreciated.

A first preliminary analysis with 8 patients showed an **improvement in the MIMICS group** in their walking ability after the 4-week intervention. They advanced from no walking at the beginning of the study to walking with continuous physical assistance at the end of the intervention (Figure 12). Two weeks after the intervention they were able to walk with light touch to assist balance or coordination. The Lokomat group did not reach the FAC level 1. Furthermore the **MIMICS group augmented their walking speed** over 10 meters (Figure 13).

The overall analysis will be presented in the final project management report.

Functional Ambulation Classification (FAC)



FAC: 0=Nonfunctional Ambulation, 1=Ambulator-Dependent for Physical Assistance-Level II, 2=Ambulator-Dependent for Physical Assistance-Level I, 3=Ambulator-Dependent for Supervision, 4=Ambulator-Independent Level Surfaces Only, 5=Ambulator-Independent.

Figure 12 Functional Ambulation Classification (FAC) before and at the end of the intervention and at a 2-week follow up.

Walking speed (10m walk test)

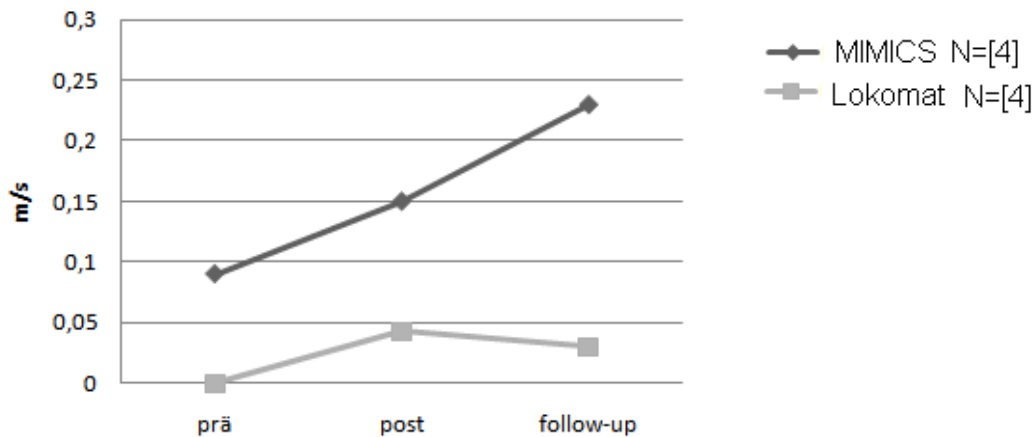


Figure 13 Walking speed (10m walk test) before and at the end of the intervention and at a 2-week follow up.

3 HapticMaster and Armeo

3.1 HapticMaster and Armeo platform

3.1.1 Scenarios

Scenarios for the HapticMaster must **train reaching, grasping and lifting movement** while keeping the subject as **motivated and engaged** as possible. To this end, three scenarios of increasing complexity were designed. All three can provide active haptic support to the subject.

3.1.1.1 *Apple scenario*

The first scenario is a **simple pick-and-place task** in which apples fall from a tree onto the ground (Figure 14). The subject needs to pick up the apples and place them into a crate. The task involves no time limitations; the subjects can proceed as quickly or as slowly as they desire.



Figure 14 The apple pick-and-place scenario for the HapticMaster, with the apple (lower right) and basket (lower left).

3.1.1.2 *Ball scenario*

The second scenario is a more intensive task that adds **a time constraint and a competitive element**: a ball rolls down a slope, and the subject must catch it before it reaches the bottom (Figure 15). Once the subject grasps the ball, he or she must place it into a basket above the slope. **Several task difficulty levels** were implemented, with different speeds, sizes and weights of the ball.

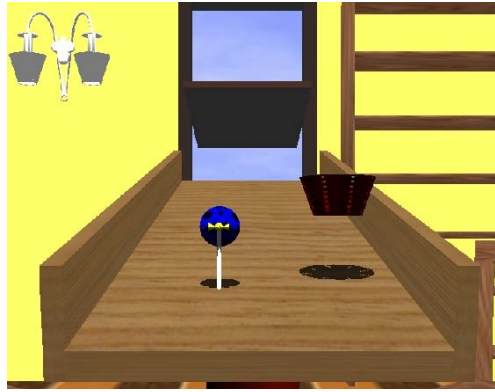


Figure 15 The ball-catching scenario, with the ball (centre, held by virtual end-effector) and basket (centre-right).

Users can choose among **different types of music** (rock, pop, folk music, classical, instrumental) depending on their **preferences** and **mood**, and **environmental sounds** are played for a more realistic experience.

3.1.1.3 *River scenario*

Based on feedback received from patient trials with the above scenarios, an extensive analysis of the principles of game design was conducted with the assistance of a psychologist. Then, a third scenario, called the river scenario, was created with the goal of **maximizing the patient's intrinsic and extrinsic motivation** by utilizing the principles of computer game design. The scenario has three subsequent repeating steps.

- The first step is a **physical activity**. A bottle is floating down a river, and the subject has to catch it by moving the arm and grasping it.
- The second step is a **mental activity**. The subject is presented with a quiz question from the bottle. The questions are of various types and difficulty levels.
- The third step is again a **physical activity**. The quiz question has two possible answers, and the subject must choose between them by placing the bottle into a basket on the left or right side of the screen where the correct answer is located. For instance, if the user thinks that the answer on the left is correct, he or she places the bottle into the basket on the left.

This creates a **combination of physical and cognitive activity in order to maintain the user's engagement**.

Screenshots of the scenario are shown in Figure 16 and Figure 17. In Figure 16, the user has picked up the bottle and received a question. In Figure 17, the user has not picked up the bottle yet.



Figure 16 The river scenario, with the bottle (centre), baskets (left and right of bottle), and question with two possible answers (top). The subject's current score is shown in the bottom left.



Figure 17 The river scenario, with the bottle (centre) and the circle-with-squares representing the user's current position (above and to the left of bottle). The two baskets wait on the far left and right for the user to pick up the bottle.

The scenario has many features that can be adjusted to better suit the current subject: the level of haptic assistance, the physical difficulty level (adjusted by changing the speed of the bottle, the height of the basket etc.), the question type and difficulty level, the type of music etc.

3.2 Clinical evaluation

Table 2 lists all the studies conducted at UL as part of MIMICS, in chronological order. For each study, it lists the question that we wished to answer with the study, whether it was reported in a previous deliverable, and whether it was a clinical study. Only clinical studies are described in this deliverable.

Table 2 Upper extremity studies conducted at UL

Question we wished to answer	Clinical study?	Reported in previous deliverables	In this deliverable
Can we see any psychophysiological responses with our equipment?	no	D3.1, D6.2 (2008)	no
How are psychophysiological responses affected by physical workload?	no	D4.2, D6.2 (2008)	no
Do subacute stroke patients exhibit useful psychophysiological responses?	yes	D4.2 (partially), D6.2 (2009 - briefly), periodic report 2	3.2.1
Do chronic stroke patients exhibit useful psychophysiological responses?	yes	D4.2 (methods) D6.2 (month 30 - very briefly)	3.2.2
How do different types of haptic assistance affect subjects' biomechanical responses?	yes	D3.2, D6.2 (month 30 - briefly)	3.2.3
How are biomechanical parameters affected by different object weights and trajectories?	no	periodic report 2	no
How is skin conductance affected by sound during rehabilitation?	no	D6.2 (2009), periodic report 2	no
Can reinforcement learning be used to directly control physiology?	no	D3.2, D6.2 (2009), periodic report 2	no
How is patient motivation affected in the River scenario by two different rehabilitation platforms?	yes	D4.3 (methods), D6.2 (2010 1/2 - briefly)	3.2.4
How is patient motivation affected by the complexity and features of a virtual rehabilitation scenario?	yes	none	3.2.5
Can discriminant analysis be used for data fusion and assessment of task suitability in healthy subjects?	yes	D3.2, D6.2 (2009 - briefly), periodic report 2 (briefly), D6.2 (month 30 - briefly)	3.2.6
Can discriminant analysis be used for data fusion and assessment of task suitability in hemiparetic patients?	yes	D3.2 (partially), D6.2 (month 30 - very briefly)	3.2.6
How useful are psychophysiological measurements in a feedback loop for control of task difficulty?	yes	none	3.2.6

3.2.1 Subacute stroke patients' psychophysiological responses to rehabilitation

3.2.1.1 Goal

It is well-known that stroke patients exhibit long-lasting abnormalities in autonomic nervous system responses. Because of this, we first wished to **see if any useful information can be obtained from stroke patients' psychophysiological responses** in a clinical rehabilitation setting. Since the principal target group of the MIMICS project is **subacute stroke patients**, they were also the focus of the first clinical study.

3.2.1.2 Materials and methods

Twenty-three subacute stroke subjects and twenty-three control subjects participated in this study. The **stroke group** consisted of 16 males and 7 females (age 51.0 ± 13.3 years, age range 23–69 years). They were diagnosed with subarachnoid hemorrhage (4 subjects), intracerebral hemorrhage (9 subjects) or cerebral infarction (10 subjects). As a result of the stroke, 13 suffered from hemiparesis of the left side of the body and 10 suffered from hemiparesis of the right side of the body. Time between stroke onset and the experiment session was 154 ± 79 days. The **control group** was age- and gender-matched to the stroke group. 13 performed the tasks with their left hand while 10 performed them with their right hand.

The subjects performed a **physically demanding** task with no cognitive workload (a physical control task), two difficulty levels (normal and hard) of a **physically and cognitively demanding** virtual rehabilitation task (the ball scenario), and a physically

undemanding but **cognitively demanding** task (the Stroop word-colour interference task). Four psychophysiological responses (heart rate, skin conductance, respiration and peripheral skin temperature) were recorded in addition to the Self-Assessment Manikin questionnaire. A photo of a patient working with the ball scenario is shown in Figure 18.

The **experiment protocol** was as follows. Upon arrival, subjects were informed of the purpose and procedure of the experiment, then signed an informed consent form. Then, they were seated in front of the robot. The affected arm was strapped into the cuffs and grasping device, and the physiological sensors were attached. The normal virtual rehabilitation task was demonstrated, and subjects were allowed to practice it briefly. Then, subjects went through the following procedure: rest period, physical control task, rest period, normal virtual rehabilitation task, harder virtual rehabilitation task. After the harder virtual rehabilitation task was completed, the Stroop task was explained and demonstrated, and a few minutes were once again given to practice. Then, subjects went through a rest period followed by the Stroop task. After the Stroop task, the experiment was concluded and a brief informal interview was conducted. Each task and rest period lasted three minutes.



Figure 18 A patient performing the virtual rehabilitation task (the ball scenario).

3.2.1.3 Results

Subacute stroke patients did display significantly weaker psychophysiological responses than controls. Most notably, resting heart rate was significantly higher in patients than in controls, and the differences in heart rate and skin temperature from baseline to task were significantly lower in patients than healthy controls. An example for skin temperature can be seen in Figure 19, where the stroke group shows nearly no difference from baseline (resting) condition to any task condition while the control group shows significant differences.

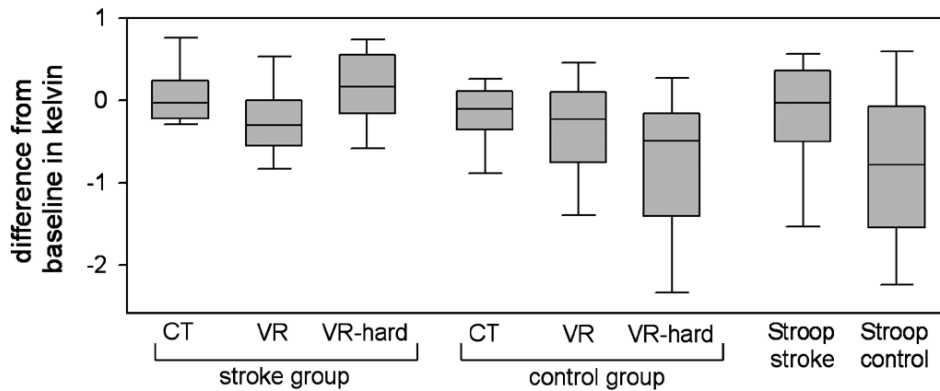


Figure 19 Differences in skin temperature from baseline to task for different groups (subacute stroke and control) and different tasks: the physical control task (CT), virtual rehabilitation task (VR), harder virtual rehabilitation task (VR-hard) and Stroop task.

Skin conductance nonetheless revealed significant differences between tasks in all groups. An example of one subject's skin conductance is shown in Figure 20 while a box plot of skin conductance level changes is shown in Figure 21. For both stroke and control groups, skin conductance was significantly higher during the normal virtual rehabilitation task than during the physical control task and significantly higher during the hard virtual rehabilitation task than during the normal virtual rehabilitation task. Additionally, **significant correlations** were found between several psychophysiological responses and results of the Self-Assessment Manikin. Most prominently, there was a significant correlation (Spearman's $\rho = 0.60$) between skin conductance response frequency and self-reported arousal for both groups.

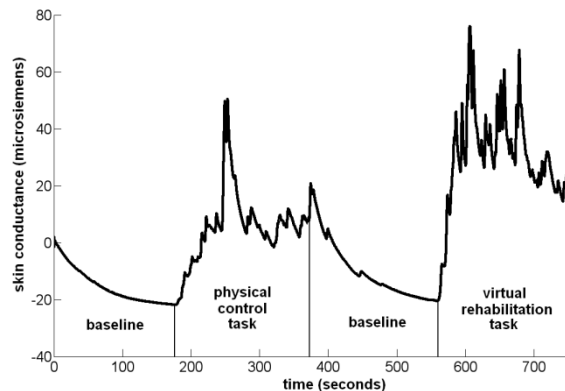


Figure 20 One patient's skin conductance during rest and during two different tasks: a simple physical control task and a more demanding virtual rehabilitation task.

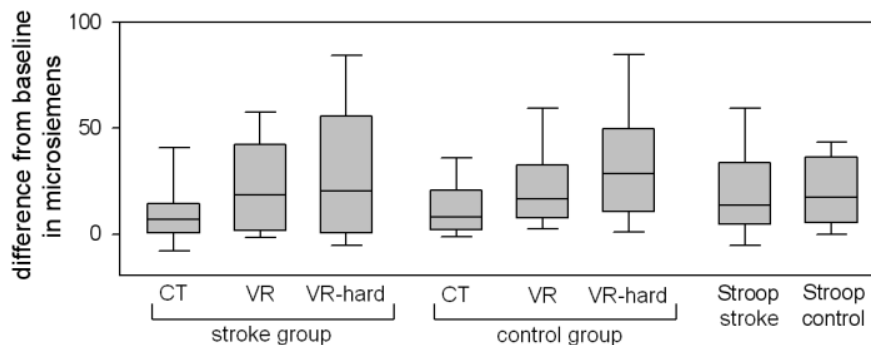


Figure 21 Differences in skin conductance level from baseline to task for different groups (subacute stroke and control) and different tasks: physical control task (CT), virtual rehabilitation task (VR), harder virtual rehabilitation task (VR-hard) and Stroop task.

Thus, we can conclude that **psychophysiological measurements do offer potential for use with subacute stroke patients in bio-cooperative rehabilitation robotics**. Detailed results of the study were published in IEEE Transactions on Neural Systems and Rehabilitation Engineering (Novak et al., Psychophysiological responses to robotic rehabilitation tasks in stroke, 2010).

3.2.2 Chronic stroke patients' psychophysiological responses to rehabilitation

3.2.2.1 Goal

Having examined the psychophysiological responses of subacute stroke patients, we also wished to see whether or not **psychophysiological responses of chronic stroke subjects**, who have had time to partially recover from the stroke, are **different from those of subacute stroke patients and healthy controls**.

3.2.2.2 Materials and methods

Due to low availability of chronic stroke subjects in Ljubljana, only **ten chronic stroke** subjects participated in the study. There were 8 males and 2 females (age 44.0 ± 14.9 years, age range 29–66 years). They were diagnosed with intracerebral hemorrhage (6 subjects) or cerebral infarction (4 subjects). As a result of the stroke, five suffered from hemiparesis of the left side of the body and five suffered from hemiparesis of the right side of the body. The time between stroke onset and the experiment session ranged between nine months to over five years, but exact dates were not available for all subjects.

The experiment session was identical to that from the previous study: a **physically demanding** task with no cognitive workload (a physical control task), two difficulty levels (normal and hard) of a **physically and cognitively demanding** virtual rehabilitation task (the ball scenario), and a physically undemanding but **cognitively demanding** task (the Stroop word-colour interference task). Four psychophysiological responses (heart rate, skin conductance, respiration and peripheral skin temperature) were recorded in addition to the Self-Assessment Manikin questionnaire. The measured psychophysiological responses were

compared to responses measured during the previous study with subacute stroke subjects and healthy controls.

3.2.2.3 Results

The analysis of psychophysiological responses suggests that **chronic stroke subjects also have weaker psychophysiological responses than healthy subjects, though not as weak as subacute stroke subjects**. This is in agreement with previous studies performed in non-rehabilitation settings.

For instance, resting heart rate of chronic stroke subjects is somewhere between the resting heart rate of subacute stroke subjects and controls (Figure 22). Similarly, chronic patients exhibit a decrease in skin temperature as a response to the hard virtual rehabilitation task (unlike subacute patients), but this decrease is not as large as it is in healthy controls (Figure 23). Finally, the correlation (Spearman's rho) between skin conductance response frequency and self-reported arousal in the virtual rehabilitation task is 0.60 for chronic patients, which is remarkably close to the values for subacute patients (0.59) and healthy controls (0.60).

However, due to the low number of chronic subjects (N = 10), these differences were not statistically significant. Thus the results can only be considered preliminary, and a **larger number of patients would be necessary to establish definite conclusions**.

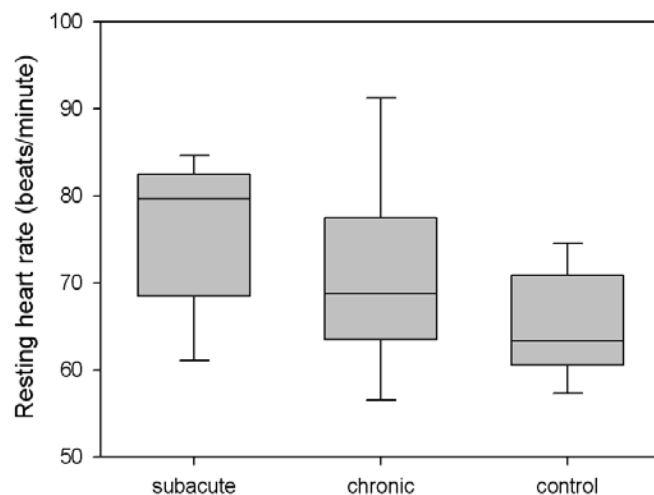


Figure 22 Resting heart rate for subacute stroke patients, chronic stroke patients and healthy controls.

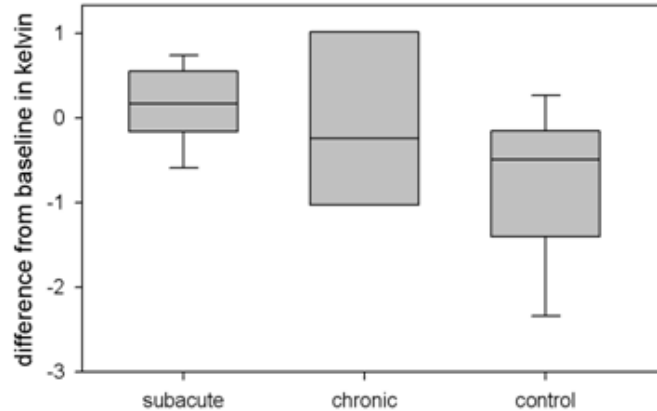


Figure 23: Differences in skin temperature from baseline to task in the hard virtual rehabilitation task for subacute stroke patients, chronic stroke patients and healthy controls.

3.2.3 Stroke patients' biomechanical responses to rehabilitation

3.2.3.1 Goal

In a follow-up study, the **biomechanical measurements** taken during the previous two studies (3.2.1 and 3.2.2) were analyzed so that we could **examine the effects of different types of haptic assistance** used during the ball scenario.

3.2.3.2 Materials and methods

Recordings from the twenty-three **subacute** stroke subjects, ten **chronic** stroke subjects and twenty-three healthy **controls** who participated in the previous two studies were analyzed from a **biomechanical** perspective. Only measurements from the normal virtual rehabilitation task (**the ball scenario**) were used. The analyzed measurements included the position of the HapticMaster's end-effector, the forces applied by the patient to the end-effector and the force used by the patient to grasp the virtual ball. As an example, the grasping force is shown in Figure 24 for one patient during three phases of a pick-and-place movement.

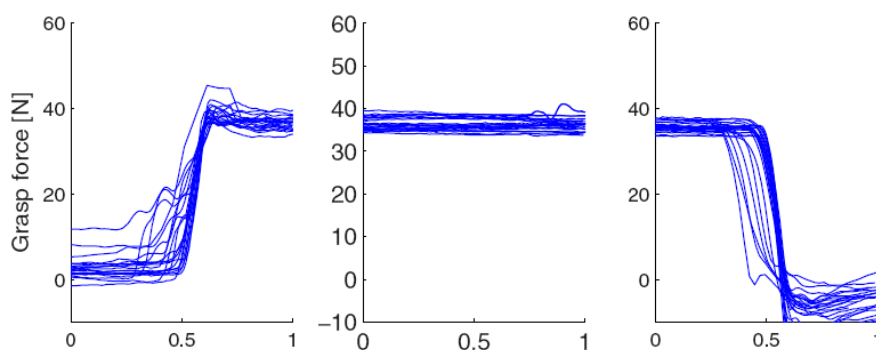


Figure 24 The grasping force during pick-and-place movement for the grasping phase (gPh), transport phase (tPh) and release phase (rPh). The movements were performed by a subacute subject who had no grasping assistance. Each line represents the force during a single pick-and-place movement.

Some of the subacute and chronic stroke subjects used **virtual force field ‘tunnels’** to perform the task since they could not complete it on their own. In these tunnels, the patient’s arm is guided along a predefined trajectory from the place where the ball is picked up to the basket where the ball needs to be dropped off. The goal of these tunnels is to allow patients to perform a task they would not be able to complete on their own while still encouraging them to exercise to the best of their abilities. An important part of the analysis was to **determine whether or not the tunnels are actually an effective way to provide a patient with haptic assistance.**

3.2.3.3 Results

Results indicated that the virtual tunnels used to provide haptic assistance do significantly **increase the number of successful pick-and-place movements**, but they also **limit the patient** and **discourage him/her from applying effort** to the task. As an example, Figure 25 shows the deviation error of the pick-and-place movements. By their very nature, the tunnels decrease the deviation error (since they prevent the arm from deviating far from a predefined trajectory), but this also proves limiting. Furthermore, Figure 26 shows that subjects who use tunnels apply very little work toward the target themselves.

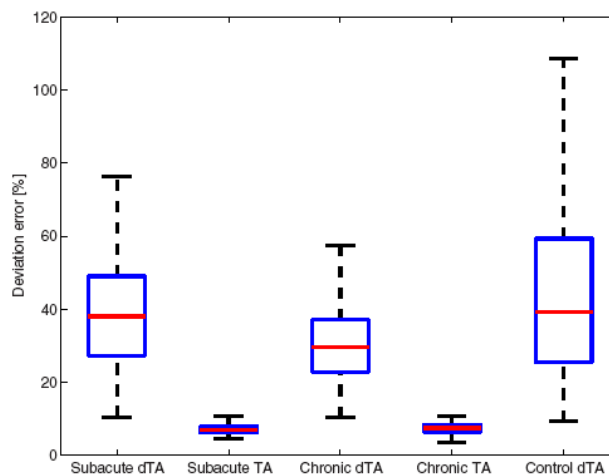


Figure 25 Deviation error of the pick-and-place movement with respect to the predefined central curve line. The results are shown for subacute, chronic and control groups with (TA) and without (dTA) tunnel assistance.

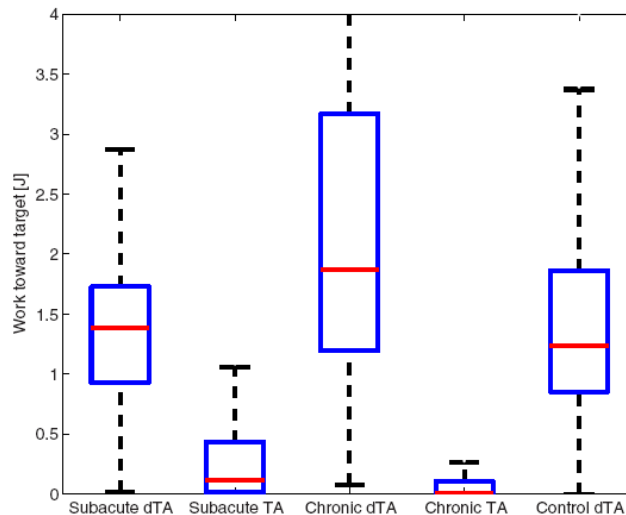


Figure 26 Comparison of the performed work toward the target during pick-and-place movement for the subacute, chronic and control groups with tunnel assistance (TA) and without tunnel assistance (dTA).

This analysis provided **valuable information about how haptic assistance should be improved** in order to emphasize patient participation in MIMICS virtual scenarios, and an adaptive haptic assistance controller was designed based on the findings. Detailed results of the analysis were published in the Journal of NeuroEngineering and Rehabilitation (Ziherl et al., Evaluation of upper extremity robot-assistances in subacute and chronic stroke subjects, 2010).

3.2.4 Patient motivation in the River scenario with two rehabilitation platforms

3.2.4.1 Goal

The goal of this study was to **analyze and compare patients' subjective and psychophysiological responses** while performing the **River** scenario on both the **HapticMaster** and **Armeo** rehabilitation platforms in order to assess patient motivation.

3.2.4.2 Materials and methods

Sixteen subacute stroke subjects participated in the study. There were 10 males and 6 females (age 46.2 ± 13.4 years, age range 22–61 years). They were diagnosed with intracerebral hemorrhage (5 subjects) or cerebral infarction (11 subjects). As a result of the stroke, eleven suffered from hemiparesis of the left side of the body and five suffered from hemiparesis of the right side of the body. Time between stroke onset and the experiment session was 128 ± 64 days.

The subjects exercised with two different difficulty levels of the **River scenario on two rehabilitation platforms**: the **HapticMaster** (with active haptics) (see MIMICS Deliverable D1.2 in general and D 1.2 chapter 4.1) and the **Armeo** (passive haptics only). Both platforms were used in the same session, one after the other in random order. The following measurements were used:

- the Self-Assessment Manikin (valence and arousal on a scale from 1 to 9),
- self-reported task difficulty (on a scale from 0 to 10),
- biomechanical measurements (forces, movements),
- psychophysiological measurements (heart rate, skin conductance, respiration and skin temperature),
- the **Intrinsic Motivation Inventory** questionnaire (Appendix I).

The **experiment protocol** was as follows: Upon arrival, subjects were informed of the purpose and procedure of the experiment, then signed an informed consent form. Then, they were seated in front of one of the haptic devices (randomly chosen). The affected arm was strapped into the device, and the physiological sensors were attached. The river scenario was demonstrated, and subjects were allowed to practice it briefly. Then, subjects went through the following procedure: rest period, one level of the river scenario (randomly chosen), rest period, the other level of the river scenario. Each of the four periods lasted three minutes. The self-assessment manikin was presented after each period, and the IMI questionnaire was presented after the second period of the river scenario. Then, the subject was transferred to the other haptic device and the rest-river-rest-river process was repeated.

3.2.4.3 *Results*

As seen in Table 3, results of the Intrinsic Motivation Inventory showed a favorable **response to the river scenario** on all subscales: interest/enjoyment, perceived competence, value/usefulness, effort/importance and pressure/tension. This shows that the river scenario is highly motivating for patients. During informal interviews, patients with a **higher level of physical impairment showed a marked preference for the HapticMaster**. Additionally, patients felt that grasping was better-implemented on the HapticMaster.

There were **no statistically significant self-reported, psychophysiological or biomechanical differences between the two platforms** (Table 4) except for a difference in jerk index. This difference is a result of the different construction of the HapticMaster and Armeo and has no practical bearing on rehabilitation. Thus, results suggest that **both platforms are useful rehabilitation tools** for patients who do not require active robotic assistance.

When evaluating these results, one important factor must be taken into account: all **patients participating in the study were able to perform all actions in the river scenario by themselves, without robotic assistance**. Those with a higher level of impairment, however, preferred the HapticMaster for the additional support. Thus, it is possible that the HapticMaster, which offers active haptic assistance, would be viewed as a more appropriate rehabilitation platform than the Armeo if a strongly impaired group of patients had participated in the study. In this case, measurements would likely have showed significant differences between the two platforms.

Table 3 Intrinsic Motivation Inventory results for both the HapticMaster (HM) and Armeo, as well as the maximum possible value for all subscales. There are no significant differences between the two platforms.

	max	HM	ARMEO
interest/enjoyment	35	27.3	26.6
perceived competence	28	21.7	22.1
effort/importance	28	23.6	24.3
pressure/tension	35	14.1	15.3
value/usefulness	35	28.3	29.3

Table 4 Results of self-reported, biomechanical and psychophysiological measurements in the HapticMaster (HM) and Armeo. Self-reported and psychophysiological values are reported as difference from baseline while biomechanical values are reported as actual values. Only the jerk index shows a significant difference ($p < 0.001$) between the two platforms.

VARIABLE	HM	Armeo
valence (scale 1-9)	0.2 ± 1.1	0.2 ± 0.6
arousal (scale 1-9)	2.7 ± 2.5	2.6 ± 2.4
difficulty (scale 0-10)	5.1 ± 2.3	4.8 ± 1.9
catching efficiency (%)	87 ± 12	86 ± 10
pick & place efficiency (%)	95 ± 8	98 ± 4
pick & place time (s)	9.2 ± 3.1	9.6 ± 3.5
deviation error (%)	47.0 ± 18.5	64 ± 39
jerk index (%) ***	45 ± 17	142 ± 57
mean HR (bpm)	3.0 ± 4.6	3.3 ± 4.1
max-min HR (bpm)	0.2 ± 5.7	-0.3 ± 6.7
SDNN (%)	10 ± 40	0 ± 30
RMSSD (%)	6 ± 33	4 ± 35
pNN50	-0.01 ± 0.09	-0.02 ± 0.09
LF/HF ratio (%)	100 ± 162	52 ± 90
HF power (%)	4 ± 32	10 ± 25
LF power (%)	62 ± 95	60 ± 96
mean SCL (μS)	12.0 ± 13.2	11.0 ± 22.7
SCR frequency (%)	276 ± 382	167 ± 206
mean SCR amplitude (μS)	1.2 ± 1.7	0.6 ± 1.7
mean respiratory rate (bpm)	2.1 ± 3.5	2.0 ± 2.4
SD respiratory rate (%)	66 ± 85	17 ± 66
mean temperature (K)	-0.1 ± 0.5	0.2 ± 0.4
final temperature (K)	-0.3 ± 0.6	0.1 ± 0.5

3.2.5 Effects of type of virtual scenario on patient motivation

3.2.5.1 Goal

Having found that the river scenario is highly motivating for patients, we wished to see if this motivation is caused by the complex elements of the scenario or whether it is simply a consequence of any robot-assisted rehabilitation. Specifically, we wanted to **see if a simpler scenario would also elicit a high level of motivation.**

3.2.5.2 Materials and methods

Six subacute stroke subjects participated in this study (all male, age 59.3 ± 10.6 years, age range 48–77 years). All were diagnosed with cerebral infarction. As a result of the stroke, five suffered from hemiparesis of the left side of the body and one suffered from hemiparesis of the right side of the body. The time between stroke onset and the first experiment session was 233 ± 103 days.

In addition to normal therapy, each subject also participated in **four robot-assisted rehabilitation sessions**: two with the **apple scenario** (a simple scenario developed at the very beginning of MIMICS) and two with the **river scenario** (a complex scenario incorporating all the features developed in MIMICS). Sessions were held twice a week (once with one scenario, once with the other) for two weeks. The session was led by the therapist, who adjusted the parameters of the scenarios (level of haptic assistance, type of music, task difficulty level) according to the patient's preference and his/her own professional opinion. The **Intrinsic Motivation Inventory** (IMI – Appendix I) was filled out after each session. Additionally, **skin conductance and peripheral skin temperature** were recorded throughout the sessions. After the last session, subjects received an **additional questionnaire** that asked them to express their preferences regarding the scenario/s (including specific features of the river scenario).

Since the goal was to keep the robot-assisted rehabilitation sessions as 'natural' as possible, there was **no tightly defined experiment protocol**. Each session consisted of a three-minute baseline (rest) period followed by the subject exercising with the scenario for as long as he wanted (five-minute minimum).

3.2.5.3 Results

No significant differences between the two scenarios were found in responses to the IMI. However, the IMI, though it had been previously validated for use in rehabilitation, was found to be rather complicated for patients – especially statements that include a negative. For instance, patients had trouble understanding that answering 'Strongly disagree' to the statement 'I was not able to perform the task well' means the same thing as 'I was able to perform the task well'. Thus, **the IMI may not be suitable for future studies with stroke subjects.** In the final

questionnaire, **four out of six subjects strongly preferred the river scenario**, one had no preference, and one (who had trouble comprehending the questions posed in the river scenario) preferred the apple scenario (as shown in Figure 27). Results from some of the other questions are illustrated in Figure 28. Analysis of psychophysiology showed that the **river scenario elicits a significantly higher increase in skin conductance**, though this may not necessarily reflect higher motivation. These results, although limited by a small sample size, suggest that **complex, game-like scenarios can increase patient motivation** by providing an interesting challenge.

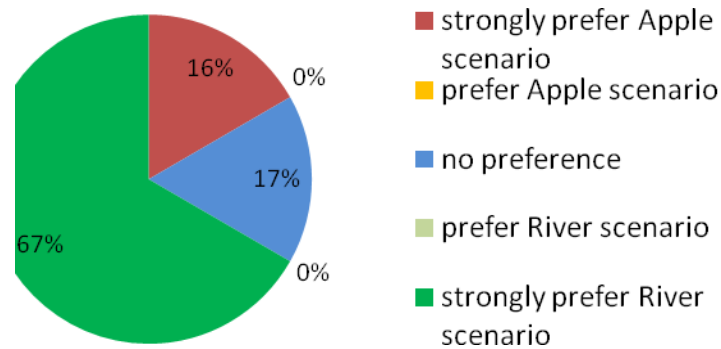


Figure 27 Patients' scenario preferences.

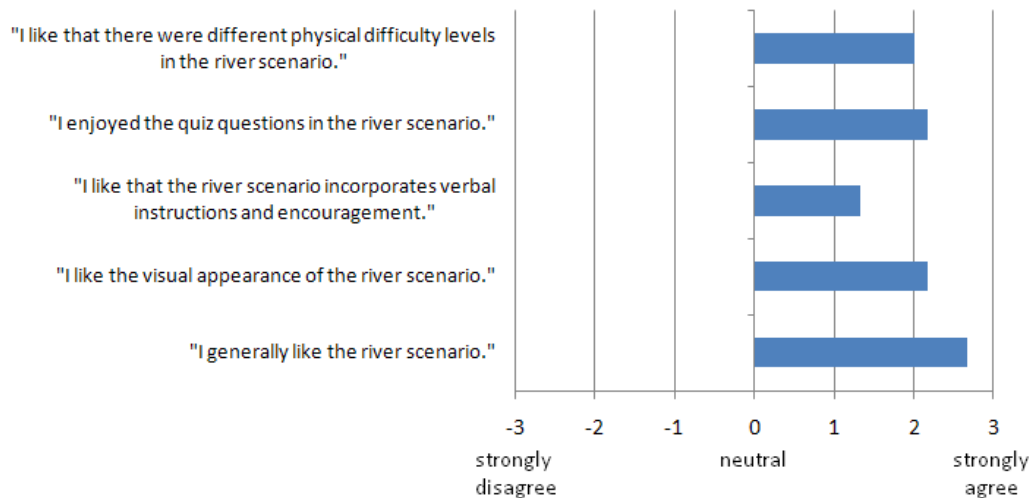


Figure 28 Patient responses to the final motivation questionnaire.

3.2.6 Adaptive discriminant analysis: open-loop and closed-loop control

3.2.6.1 Goal

Having previously established that psychophysiological responses can provide information about the patient's psychological state during upper extremity rehabilitation, the goal was to **fuse different measurements** into an estimate of how appropriate the current task difficulty is for the patient. Once this estimate is made, it can be used to **dynamically adjust the task difficulty** in order to make it more appropriate for the patient.

3.2.6.2 *Materials and methods*

The **ball scenario with six different difficulty levels** was used in the study. Difficulty was manipulated by adjusting the speed and size of the ball. The highest difficulty level featured very small, fast balls while the lowest level featured very large, slow balls. The study was divided into two phases: the **open-loop phase** (where task difficulty is adjusted manually by the subject and experiment supervisor) and the **closed-loop phase** (where task difficulty is adjusted by the biocooperative controller). The open-loop phase was conducted first, with the goal of obtaining a larger set of data for analysis and for training a biocooperative controller. After the conclusion of the open-loop phase, linear discriminant analysis was used on the measured data set in order to **build a set of rules** for automatically determining whether the task is too easy or too hard for the patient. An advanced variant of linear discriminant analysis, Kalman adaptive linear discriminant analysis, was used to adapt to intersubject differences. In the second, **closed-loop phase** of the study, the previously developed rules were implemented in a biocooperative controller that automatically adjusted task difficulty based on psychophysiological, biomechanical and task performance measurements.

The **experiment procedure for both phases was similar**. Upon arrival, subjects were informed of the purpose and procedure of the experiment, then signed an informed consent form. Then, they were seated in front of the robot. One arm (the paretic arm for patients, the right arm for healthy subjects) was strapped into the cuffs and grasping device, and the physiological sensors were attached. The third difficulty level of the task was demonstrated, and subjects were allowed to practice it briefly. After practice, the subject rested for two minutes while baseline physiological measurements were recorded. Then, the subject began performing the task at level 3, 4 or 5 (randomly chosen). After two minutes of performing the task at that difficulty level, the task was paused briefly and the subject was asked whether he or she would prefer the difficulty of the task to increase or decrease. Subjects were not given the option to stay at the same difficulty level. In the **open-loop phase**, once the subject had stated his or her preference, the difficulty changed by one or two levels in the direction **chosen by the subject**. In the **closed-loop phase**, the difficulty changed in the direction **chosen by the biocooperative controller**. After task difficulty was changed, the task began again at the new difficulty. In total, the subject went through six two-minute periods, with the subject's preference noted and the difficulty changing after each one. After the final task period, the experiment was concluded.

Twenty-four healthy subjects (20 males, 4 females, age 31.1 ± 10.9 years, age range 21-61) and eleven hemiparetic patients (8 males, 3 females, age 43.2 ± 13.5 years, age range 22-69) participated in the open-loop phase of the study. Ten healthy subjects (9 males, 1 female, age 33.9 ± 12.6 years, age range 22-62) and six hemiparetic patients (4 male, 2 female, age 58.3 ± 6.3 years, age range 54-67) participated in the closed-loop phase of the study.

The **patients in the open-loop group** were hemiparetic as a result of intracerebral hemorrhage (3 subjects), cerebral infarction (4 subjects), or surgery of a neoplasm of the brain (4 subjects). Time since stroke onset or surgery was 216 ± 228 days (minimum 14, maximum 749). Six suffered from hemiparesis of the left side of the body and five suffered from hemiparesis of the right side of the body. The **patients in the closed-loop group** were hemiparetic as a result of subarachnoid hemorrhage (1 subject), intracerebral hemorrhage (2 subjects), cerebral infarction (2 subjects), or surgery of a neoplasm of the brain (1 subject). Time since stroke onset or surgery was 166 ± 34 days (minimum 110, maximum 202). Score on the FIM was 108 ± 5 . Three suffered from hemiparesis of the left side of the body and three suffered from hemiparesis of the right side of the body.

3.2.6.3 Results – open-loop phase

Results for leave-one-out cross-validation in the **open-loop phase** are shown in Table 5 for **healthy subjects** and **patients**. Furthermore, Table 6 shows results for leave-one-out cross-validation in the open-loop phase when discriminant functions are **built using data from healthy subjects, then tested on patient data**. The accuracy rate is defined as the percentage of times that the discriminant function correctly predicts the subject's preference regarding task difficulty (too easy / too hard).

Table 5 Accuracy rates for open-loop cross-validation of nonadaptive and adaptive linear discriminant analysis on different types of input data. Discriminant functions for each group (healthy or patients) were built using only data from that group.

	performance	biomechanics	psychophysiology	all
healthy – nonadaptive LDA	81.9	75.0	60.4	84.7
healthy - adaptive LDA	82.6	80.6	76.4	84.7
patients – nonadaptive LDA	81.8	75.8	60.6	89.4
patients - adaptive LDA	81.8	75.8	68.2	89.4

Table 6 Accuracy rates for open-loop cross-validation of nonadaptive and adaptive linear discriminant analysis on different types of input data. The discriminant functions were built using data from healthy subjects, then tested on patient data.

	performance	biomechanics	psychophysiology	all
patients – nonadaptive LDA	83.3	65.2	53.0	81.8
patients - adaptive LDA	83.3	68.2	66.7	81.8

The above results suggest that **psychophysiological responses are rather inaccurate** on their own, though the Kalman **adaptive discriminant analysis noticeably improved their usefulness**. Additionally, Table 5 shows that **psychophysiological rules trained on healthy subjects cannot be transferred to patients** without a marked decrease in accuracy. However, as is evident from Table 4, **psychophysiological measurements do provide some supplementary information** that can improve closed-loop control, though it is questionable whether this information is sufficient to justify the inclusion of psychophysiological measurements in the system.

The **usefulness of adaptive discriminant analysis when using psychophysiological measurements** was examined in a follow-up analysis where nonadaptive and adaptive discriminant analysis were compared as functions of time.

The result is shown in Figure 29 and shows a marked increase in classifier accuracy rate after the first time period. The analysis was performed on healthy subjects due to a larger sample size.

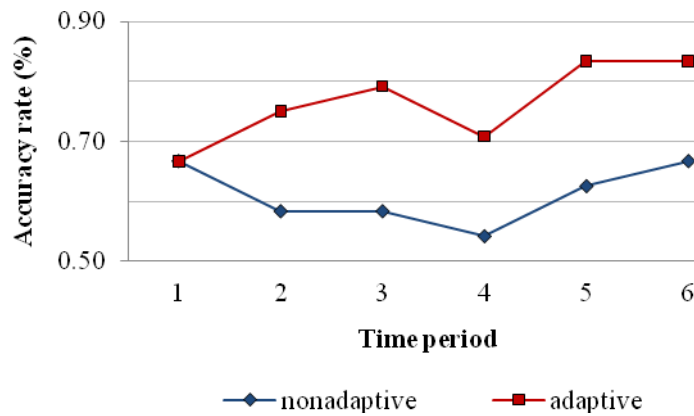


Figure 29 Accuracy rate as a function of time period for open-loop cross-validation of nonadaptive and adaptive LDA. The inputs are psychophysiological features from healthy subjects.

In a second follow-up analysis, we examined how the accuracy rate of nonadaptive discriminant analysis increases as the size of the available training set increases. Once again, the analysis was performed on healthy subjects due to a larger sample size. The result is shown in Figure 30. It is evident that, **when all types of input data are included, the accuracy rate steadily increases with the size of the training set**. This can also be seen for biomechanical measurements while the accuracy rate for performance and psychophysiology is only slightly affected by the size of the training set.

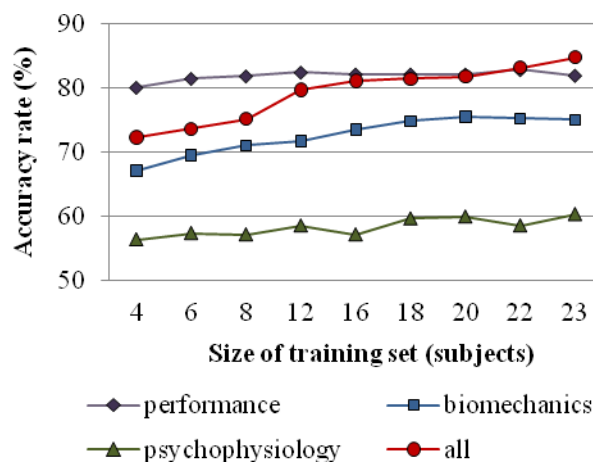


Figure 30 Accuracy rate as a function of training set size for different types of input data in open-loop cross-validation. Accuracy rate is taken for the best nonadaptive method. All data are from healthy subjects.

3.2.6.4 Results – closed-loop phase

In the **closed-loop phase**, discriminant analysis using all types of data as input **correctly predicted** 88.3 % of healthy subjects' preferences as well as 88.9 % of patients' preferences and **adjusted task difficulty** accordingly.

In a **follow-up offline analysis**, the closed-loop data was also passed through the most accurate discriminant function based only on performance data (also trained using data from the open-loop phase). **Performance data** yielded an accuracy rate of 86.7 % for healthy subjects and 83.3 % for patients. Once again, it is evident that the inclusion of psychophysiological measurements increases the accuracy of the biocooperative controller, though it is uncertain whether this increase is sufficient to justify the increased complexity of the system. For an example of psychophysiology increasing accuracy, see Figure 31.

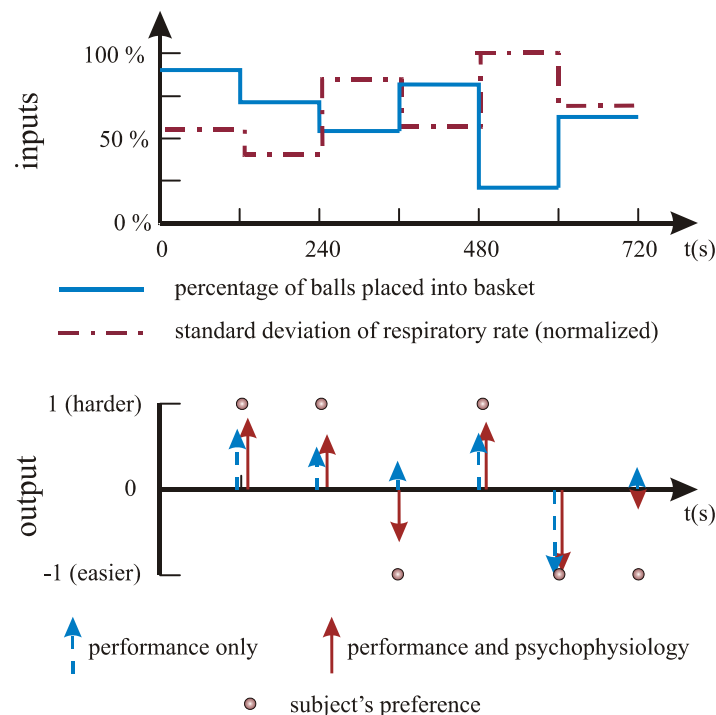


Figure 31 One hemiparetic patient in the closed-loop phase: two input features (one performance, one psychophysiological), the output of the discriminant function, and the subject's preferences. High performance and a low *standard deviation of respiratory rate* (even, regular breathing) indicate an easy task. For the first, second, fourth and fifth task periods, task performance would have been sufficient to change the difficulty. During the third period, task performance is moderately high, but breathing becomes very uneven, indicating stress. If only task performance had been taken into account in this case, the incorrect decision would have been made (the patient was successful at the task, but was stressed and wanted difficulty to decrease). During the last period, both performance and psychophysiology are unreliable, and the patient stated that he would most prefer difficulty to stay the same.

Thus, a **biocooperative feedback loop** for dynamic difficulty adjustment in upper extremity rehabilitation was **successfully designed and tested** in a clinical setting.

A manuscript with a detailed description of the study and its results was submitted to IEEE Transactions on Neural Systems and Rehabilitation Engineering.

3.2.7 Evaluation of the River scenario

The river scenario with questions (“question task”) was not suitable for patients who had problems with language. That’s why UL designed an additional nonverbal and graphical version of the scenario (“picture task”). In a study NKBA intended to evaluate the two river scenarios with subacute stroke patients using the Armeo. The aim of the study was to assess the immediate influence of a cognitive task integrated in a motor VR-exercise on motor output and arousal. Task performance, movement quality, psycho-physiological responses and motivation were measured and correlated with clinical scores and neuropsychological tests. Furthermore we expected different task preference depending on the cognitive impairment of the patient. For the study UL implemented another third version with arrows instead of questions or pictures (“baseline task”).

A questionnaire was designed to assess patient’s motivation, preference and effort. Patients rated the “question task” as most enjoyable and motivating followed by the “picture task” (Figure 32). Furthermore the “questions task” was the cognitive most challenging version. The physical effort was comparable for all the river versions.

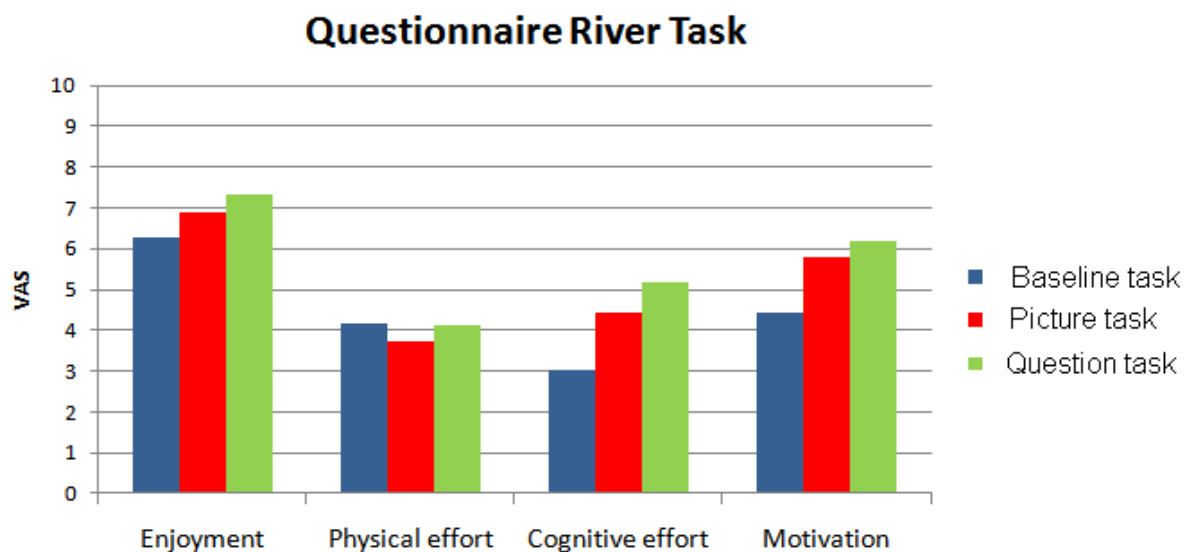


Figure 32 Self-designed questionnaire presented as visual analogue scale (VAS) assessing enjoyment, physical effort, cognitive effort and motivation after performing the three versions of the river scenario [N=9].

Analysis of kinematics and dynamics, task performance and psycho-physiological measurements are running. Clinical scales and tests are correlated to the outcome measures.

3.2.8 Study on Fitt’s law using Armeo

The goal of MIMICS is to enhance patient motivation during rehabilitation. Research has shown that people who believe that they are competent or successful in an activity remain engaged and motivated over a longer period of time. In our view, this can be transferred to rehabilitation if an augmented feedback application provides a mechanism that adjusts the difficulty of an exercise to the capabilities of the patient. Adjusting the difficulty however can only be achieved if the application is aware of a patient's current motor performance. For upper-extremity rehabilitation we therefore conducted a study using Armeo. We tried to verify if the well established empirical formula Fitt's Law can be used to assess patient motor capabilities and if the results of this assessment can then be used to adapt the difficulty of an exercise i.e. influence the success rate of the patient during the exercise.

In the exercise, the patient had to move the mouse-pointer using his arm from randomly placed, circular start locations to randomly placed, circular target location of different sizes and click on the latter by closing the hand. The question was if Fitt's Law would help to estimate the time that the patient would need to fulfill this task.

In order to verify the mechanism, a study was conducted which consisted of an assessment phase using Fitt's Law and three different conditions of varying difficulty.

- (1) The assessment phase consisted of measuring a block of 50 movements. A linear regression on the acquired data then gave the slope and intercept of Fitt's Law which were used to set the movement times during conditions 2-4.
- (2) An easy condition where the patient had double the time then what was estimated for the movement.
- (3) A balanced condition where the available time was equal to the estimated time.
- (4) A hard condition where patients had half the estimated time to complete the movement.

In order to verify its applicability, the experiment was carried out twice per patient. Once for the paretic and once for the non-paretic arm.

Figure 33 illustrates the success rate of a representative patient (Patient 10) i.e. the percent of trials the patient reached the target location on time, for each condition. Patient 10 showed a good linear fit of the data measured in the assessment phase for both the paretic ($r^2 > 0.8759$, Figure 33) and non-paretic ($r^2 > 0.7442$) arm. Results show a gradual decrease of the success rate for the paretic arm. In the non-paretic arm the patient was able to get 100% for the easy and balanced condition. In conclusion, the time that was calculated in the estimation based on Fitt's law adequately describes the time the patient needs to successfully reach the target. Manipulating the time limit thus yields a potential adaptive mechanism by which the success rate during the exercise i.e. the task difficulty can be adjusted.

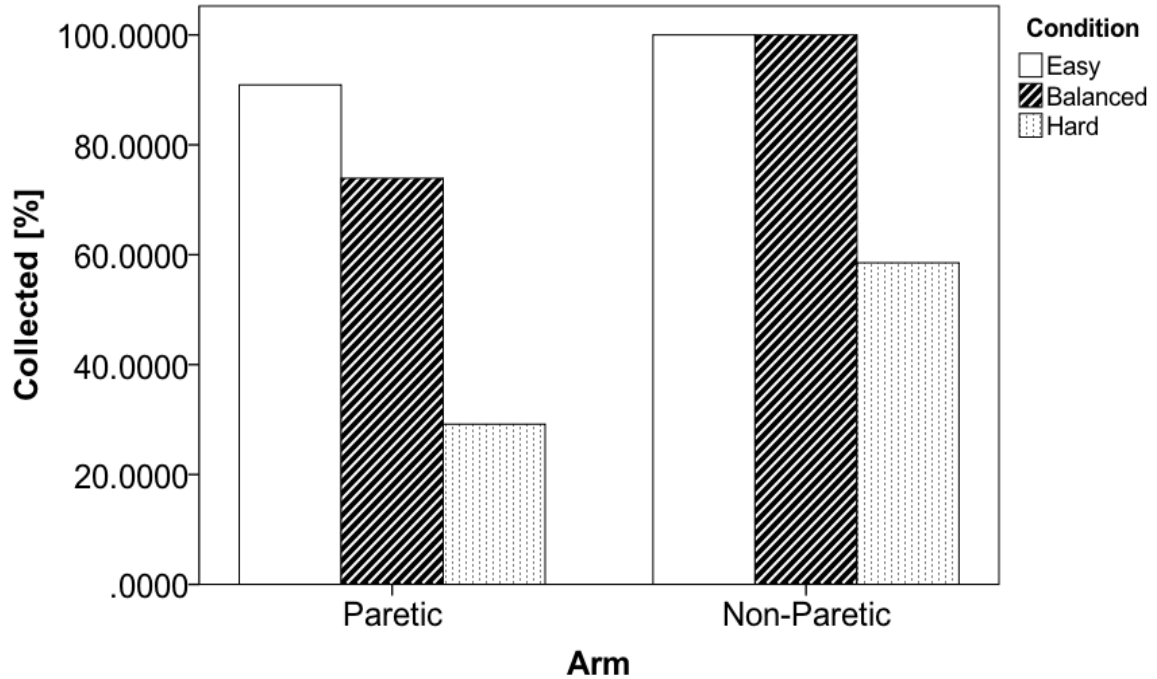


Figure 33: Successful trials for different difficulty conditions of the paretic and non-paretic arm of Patient 10 during an exercise with.

Additional measurements with more patients will further help to verify the validity and applicability to augmented feedback applications. The advantage of having such a mechanism is it's proven physiologically validity for reaching motions and its simplicity, which allows applying the mechanism to a wide range of different upper-extremity applications.

4 Future clinical trial

4.1.1 Future collaboration with UB

NKBA installed a setup with a head mounted display (HMD). UB implemented the proxemics scenario (described in 2.1.1.3) and transferred the city navigating scenario (described in 2.1.1.4) to the Lokomat. Measurements with patients using the proxemics scenario are running and experiments applying the HMD in the Lokomat using the city navigation scenario are scheduled at NKBA.

Further collaboration with UB is planned to adapt and advance the scenarios and to design HMD applications for the therapy of postural control, neglect and pusher symptoms.

4.1.2 Future extension of ongoing clinical trials

Since the MIMICS project focused on the development of technical solutions for the VR usage in rehabilitation, the work packages did not include a study with enough power to prove the superiority of the VR-exercise. NKBA plans to increase the number of stroke patients participating in the clinical study described previously up to 20 subjects till the middle of 2011.

The study aims to prove the efficacy of VR-enriched rehabilitation on the rehabilitation process and outcome. We expect higher motivation in patients performing Lokomat therapy with MIMICS-VR than in patients with conventional Lokomat therapy. As patients' motivation plays a crucial role in determining therapy outcome the objective of this study is to determine changes in several walking-related outcome measures due to VR-enriched robot aided gait therapy. We hypothesize that participants of the MIMICS-VR will improve significantly more in their walking ability (measured with the 10m walking test and the FAC) than the standard Lokomat group after 4 weeks of training (3 sessions per week). Besides the study addresses whether the therapy in VR leads to improvements in visual-spatial abilities.

Subjects are randomly assigned to either the intervention or the control group. We aim for 10 subjects in each group.

The scenarios applied in the VR-enriched therapy are the dog and collect/avoid scenario since previous testing proved them as best suitable for stroke patients. According to the activity patients are able to generate in the paretic leg, the bilateral or paretic leg control mode is applied (range of 50 biofeedback values in the paretic leg). Additionally to the 12 therapy sessions a 13th session after the intervention is scheduled, where patients from the MIMICS group receive standard Lokomat and vice versa (crossover).

Assessments (FAC, 10m walking test, dual task, 6min walking test, Ashworth Scale, VS and block design test) are done by a physiotherapist and neuroscientist in the week before the intervention, at the end of the intervention and at the follow up 2 weeks after the end of the intervention. The Intrinsic Motivation Inventory (IMI) will be collected in the first, 6th and 12th Lokomat session and in the crossover session (13th).

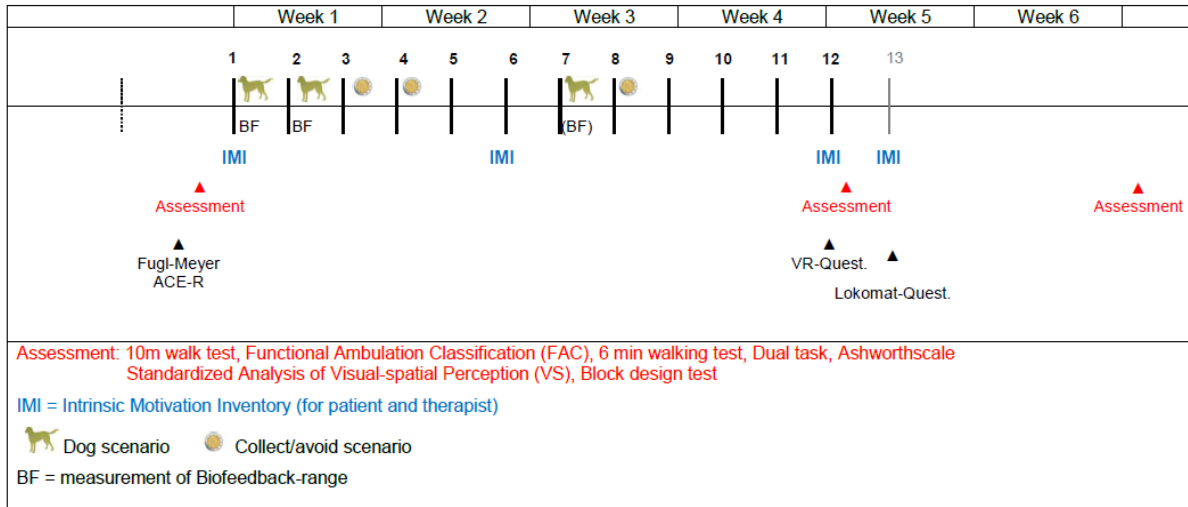


Figure 34 Application scheme of the outcome measures.

5 Conclusion and Outlook

Clinically usable systems have been developed and evaluated for upper and lower extremity devices:

ETH Zurich, HOCOMA and UB designed various virtual environments for the Lokomat. The scenarios have been clinically tested and augmented in cooperation with NKBA.

Psychophysiological recordings were found to be a useful tool to quantify cognitive load, however the clinical application is difficult. Furthermore psychophysiological measurements are not reliable enough in a clinical population of stroke victims and unsuitable to determine motivation – therefore the Intrinsic Motivation Inventory (IMI) was used to assess motivation.

ETH Zurich proved in a study that heart rate and weighted sum of the interaction torques (WIT) are appropriate ways to control patient's participation. However patients taking Beta blocking medication will not be able to exercise in HR control mode, why WIT control was chosen for a further study at NKBA comparing the activity in the paretic and non paretic leg. The study found an increased activity in the paretic leg using a unilateral control mode across the hip and knee joint of the paretic side compared to the bilateral control mode. The data support the hypothesis, that WIT control adds value to the therapeutic effect of Lokomat training.

To prove the therapeutic effects of MIMICS-VR a controlled and randomized clinical study is running. The study determines changes in various walking-related outcome measure and motivation. First interim analysis proves the approach highly valuable.

For the HapticMaster and Armeo, several scenarios with both haptic and auditory feedback loops have been implemented at UL, using a simple pick-and-place task and a more diverse ball-catching task. Based on the clinical experience with these scenarios, the next generation “River scenario” was developed to maximize motivation and combine both physical and cognitive tasks with haptic, auditory (both spoken and ambient) and visual feedback. A second, non verbal version of the River scenario was designed using pictures. Both versions were transferred to the Armeo at NKBA and a third version without an additional cognitive load was implemented. A study is running to evaluate the different river versions with stroke patients.

Our results indicate a difference in the usefulness of psychophysiological data for controlling patients' participation between the setup for the lower and the upper extremity. Reasons include more physical effort in a patient trying to learn walking compared to learning reaching and grasping. In addition, the severity of the disability is considerably different between patients unable to walk and patients with a brachial paresis being able to move their arm. Gait exercise is a more physical effort depending on support in posture etc., while dexterity training is more closely related to cognitive demands.

In conclusion, the consortium has succeeded in the timely setup of enhanced systems for upper and lower extremity rehabilitation. Clinical studies were performed

measuring motivation, psychophysiological states, activity and rehabilitation outcome.

We therefore deem the Deliverable fully achieved as envisioned by the Quality Assurance Plan as significant progress has been made in all subtasks targeted by this Deliverable.

6 References

Banz, R., M. Bolliger, G. Colombo, V. Dietz and L. Lunenburger (2008). "Computerized visual feedback: an adjunct to robotic-assisted gait training." *Phys Ther* 88(10): 1135-1145.

Bradley, M. M. and P. J. Lang (1994). "Measuring emotion: the Self-Assessment Manikin and the Semantic Differential." *J Behav Ther Exp Psychiatry* 25(1): 49-59.

Hall, E.T. 1966, *The Hidden Dimension*, Anchor Books

Kastanis, I. and Slater, M. 2010, Reinforcement Learning Utilizes Proxemics: An Avatar Learns to Manipulate the Position of People in Immersive Virtual Reality, submitted

Koenig 2010a: Koenig, A., Omlin, X., Bergmann, J., Zimmerli, L., Bolliger, M., Müller, F. and Riener R. 2010, Controlling Patient Participation during robot-assisted Gait Training. *J Neuroeng Rehabil* submitted

Koenig 2010b: Koenig, A., Omlin, X., Zimmerli, L., Sapa, M., Krewer, C., Bolliger, M., Mueller F. and Riener R. 2010, Psychological state estimation from physiological recordings during robot assisted gait rehabilitation. *JRRD* accepted

Koenig 2010c: Koenig, A. Novak, D., Pulfer, M., Omlin X., Perreault, E., Zimmerli, L., Mihelj, M. and Riener, R. 2010, Real-time closed-loop control of cognitive load in neurological patients during robot-assisted gait training. *Trans Neural Sys Rehab Eng* submitted

Malik, M. (1996). "Heart rate variability - Standards of measurement, physiological interpretation and clinical use." *European Heart Journal* 17: 28.

McAuley, E., Duncan, T., and Tammen, VV. 1989, Psychometric properties of the Intrinsic Motivation Inventory in a competitive sport setting: a confirmatory factor analysis. *Res Q Exerc Sport*, 60:48-58.

McAuley, E., Wraith, S. and Duncan, TE. 1991, Self-efficacy, perceptions of success, and intrinsic motivation for exercise. [J Appl Soc Psychol](#), 21:139-155.

Thomas, E. E., G. De Vito and A. Macaluso (2007). "Physiological costs and temporo-spatial parameters of walking on a treadmill vary with body weight unloading and speed in both healthy young and older women." *Eur J Appl Physiol* 100(3): 293-299.

Appendix I: Intrinsic Motivation Inventory

NAME:	DATE:	

Use this questionnaire to gauge your intrinsic motivation during the therapy. It consists of individual statements that you can agree or disagree with. There are no right and wrong answers to the questionnaire. Use the rating scale for each question to determine how much you agreed or disagreed with each statement during this therapy session.

1. During the therapy, I was thinking about how much I enjoyed it.

1	2	3	4	5	6	7
not at all true						very true

2. I did not feel nervous at all during the therapy.

1	2	3	4	5	6	7
not at all true						very true

3. I think I am pretty good at the therapy.

1	2	3	4	5	6	7
not at all true						very true

4. I found the therapy very interesting.

1	2	3	4	5	6	7
not at all true						very true

5. I tried as hard as I could during the therapy.

1	2	3	4	5	6	7
not at all true						very true

6. I felt very tense during the therapy.

1	2	3	4	5	6	7
not at all true						very true

7. I believe that this therapy is effective for arm rehabilitation.

1	2	3	4	5	6	7
not at all true						very true

8. It was important for me to do well at the therapy.

1	2	3	4	5	6	7
not at all true						very true

9. I think I did pretty well at the therapy, compared to other patients.

1	2	3	4	5	6	7
not at all true						very true

10. The therapy was fun to do.

1	2	3	4	5	6	7
not at all true						very true

11. I was very relaxed during the therapy.

1	2	3	4	5	6	7
not at all true						very true

12. It was important for me to do well at the therapy.

1	2	3	4	5	6	7
not at all true						very true

13. I would like to do the therapy again because it is important to me.

1	2	3	4	5	6	7
not at all true						very true

14. I enjoyed the therapy very much.

1	2	3	4	5	6	7
not at all true						very true

15. I am happy with how I could participate in the therapy.

1	2	3	4	5	6	7
not at all true						very true

16. I didn't try very hard to do well at the therapy.

1	2	3	4	5	6	7
not at all true						very true

17. I was frightened during the therapy.

1	2	3	4	5	6	7
not at all true						very true

18. I worked very hard during the therapy.

1	2	3	4	5	6	7
not at all true						very true

19. I believe this therapy could be of some value to me.

1	2	3	4	5	6	7
not at all true						very true

20. I think the therapy was boring.

1	2	3	4	5	6	7
not at all true						very true

21. I was pretty skilled at the therapy.

1	2	3	4	5	6	7
not at all true						very true

22. I believe the therapy could be beneficial to me.

1	2	3	4	5	6	7
not at all true						very true

23. I felt pressured during the therapy.

1	2	3	4	5	6	7
not at all true						very true

24. After performing the task for a while, I felt pretty competent.

1	2	3	4	5	6	7
not at all true						very true

25. I think this is an important therapy.

1	2	3	4	5	6	7
not at all true						very true