Predictors of Therapy Effects: Studies on Procedural Learning in Healthy Elderly and Stroke Patients

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Judith My Lin Lam
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Dekan: Prof. Dr. Wolfgang Rosenstiel
1. Berichterstatter: Prof. Dr. Andreas Luft
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Contents

Summary

In recent years the focus of stroke rehabilitation research has changed from approaches which only compensate patient disability to approaches which seek to understand the underlying mechanisms, in particular how to stimulate the recovery of the brain (Nadeau, 2002; Dobkin, 2004). Knowledge about plasticity of the brain, learning mechanisms, and search for predictors of functional outcome after injury and therapy drive the recent rehabilitation research in a promising direction.

Existent rehabilitation programs such as treadmill aerobic exercise training have shown group effects, but the variability of benefit within the group is quite large. Finding predictors of therapy-related benefits in treadmill training will help to adjust the program to individual stroke patients. To this end, in the first study we pooled data from two randomized controlled trials of treadmill aerobic exercise training and included clinical, demographic, and lesion-related factors as possible predictors (independent variables) of baseline performance and change of performance in fitness and walking parameters (dependent variables). We showed that patients with smaller and left-sided lesions benefit the most from treadmill training and that shorter stroke-therapy interval has a positive effect on improvement. However, these predictors only explained partly the variability in therapy effects which exists between individuals.

What other factor could influence treatment effects? In the second part of the thesis we hypothesized that deficits in learning exist that could account for treatment failures. This is particularly interesting as learning principles are applied to many training therapies. We studied feedback and reward processing that is a critical element of reinforcement learning paradigms. We investigated whether stroke patients have deficits in reward processing in a probabilistic classification learning paradigm that was first characterized in healthy elderly individuals matched for age. Deficits in how the brain is processing feedback could determine learning efficacy, hence the response to therapies that are based on learning principles.

Using fMRI, we first tested healthy seniors on the weather prediction task (WPT), a probabilistic classification task in which subjects had to predict the weather - sun or rain - based on card combinations using four tarot cards. We found that both context and feedback influence learning. Participants performed better for positive content (i.e. when sun is the outcome), and moreover positive feedback in form of a smiley face fortified the learning efficacy more than negative feedback. Comparing the feedback phase (smiley) of the WPT with the control task we observed higher activation in several brain areas: the basal ganglia (Putamen, Thalamus and NAcc) which confirms its suggested crucial role in reward learning and the sensorimotor cortex (primary motor, premotor, and somatosensory

cortex) which has not previously been shown to be activated in explicit reward learning tasks. However, the sensorimotor cortex has been shown to be highly involved in motor skill learning and habit formation, and therefore may play an important role in procedural learning per se.

Impaired procedural learning may reduce the potential for recovery. We hypothesized in our third study that stroke survivors are impaired in the WPT because of a deficit in reward processing due to disrupted reward circuits. Behavioural data showed impaired learning of the WPT in stroke patients. fMRI revealed reduced activation of reward circuits in stroke patients as compared with controls. Lesion analysis identified a link between poor learning and lesion in frontal areas, putamen, thalamus, caudate and insula. This outcome together with the fMRI results suggests that impaired procedural learning result from abnormal reward processing due to dysfunctional or lesioned areas in the reward circuits.

The deficit in reward processing in stroke patients shown here may also play a role along with the clinical factors in recovery and response to rehabilitation programs such as treadmill aerobic exercise training. This hypothesis needs to be confirmed in future rehabilitation studies which take reward or feedback as possible predictor into account to further explain the variability of effects between individuals in rehabilitation programs.

Introduction

Stroke

Stroke is world-wide one of the leading causes of life-long disabilities (www.who.int). Elderly are more often affected than younger adults (< 30 years) or children. Stroke is a result of interrupted blood supply to the brain. There are two main types of stroke: An ischemic stroke is caused by a blockage of artery, usually by a clot (thrombotic or embolic), whereas a haemorrhagic stroke results from a burst of a blood vessel resulting in a leakage of blood into the brain. The latter is less frequent but more often mortal. The undersupply of oxygen carried by the blood caused by blockage or leakage leads to dysfunctions such as motor disability, learning impairment, attention deficits, aphasia, neglect and other cognitive impairments, depending on which brain areas are affected.

It is essential to provide an acute treatment immediately after the event. Stroke units, now often incorporated in hospitals, consist of a multidisciplinary team including neurologists, specialized nurses, physiotherapists, speech therapists and other experts. Since stroke units have been established, the mortality and length of hospitalization has been reduced (Kollen et al., 2006). While some patients can recover almost entirely in the first few weeks to months, still half of the survivors suffer from impairments in movement, speech or language, vision or cognition (e.g.depression (Dafer et al., 2008)). Recovery and rehabilitation is dependent on the capacity of the brain to reorganize existing structures and connections between brain areas (Ward, 2005). Particularly the lesioned brain is "preparing" for changes by allocating cellular substrates (i.e. increased dendritic spines (Ward, 2005)) or molecular substrates (i.e. re-emergence of developmental proteins (Pearson-Fuhrhop et al., 2009)). Also different brain areas compensate and undertake the function for the lesioned area (Nudo, 2003). These changes have been observed in spontaneous recovery as well as driven by therapies (Baron et al., 2004).

Rehabilitation after stroke beyond the time frame of spontaneous recovery is of high interest. Although it has been postulated that the rehabilitation phase is limited to several months after stroke (Jørgensen et al., 1995), recently more and more randomized clinical trials have shown that even long after stroke (i.e. in the chronic phase > 6 months), patients can relearn skills and gain more independence through several therapy forms (Ferrarello et al., 2011; Luft et al., 2004c, 2008). Rehabilitation programs for motor impairments are numerous and are quite well tested: occupational therapy (Legg et al., 2006), constrained induced movement therapies for arms and hands (CIMT, (Nijland et al., 2011)), bilateral arm training (Luft et al., 2004c) and treadmill aerobic exercises (TAEX, (Luft et al., 2008; Ivey et al., 2008; Macko et al., 2005)) for the lower extremities. On the other hand studies about the rehabilitation of cognitive functions, e.g. learning and mem-

ory, neglect and attention are quite scarce (Langhorne et al., 2011).

Prescribing rehabilitation programs to individual stroke patients is part of the daily work of clinicians. Although the numerous therapy forms mentioned above show significant group effects, it is of high interest to identify the relevant factors which explain the various effect of therapies on individuals. Identifying these factors might help to adjust the rehabilitation programs to the individual needs.

Learning

Current literature on learning and long term memory distinguishes between explicit and implicit (or declarative vs. non-declarative) learning. The scheme of Squire and Zola (1996) shown in Figure 1 is still valid with some modifications.

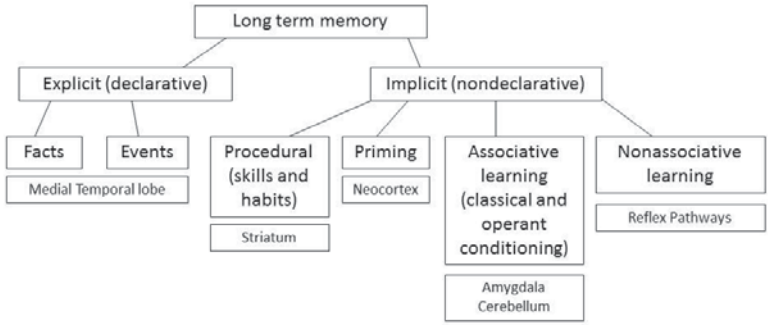

Figure 1. *Learning scheme adapted from Squire and Zola (1996)*

Explicit memory is what most people refer to when talking about memory. Explicit learning is the ability to memorize facts (semantic memory) and to put personal events into an original context (episodic memory). Explicit memory can be verbalised, hypothesis-testing-driven and flexible, that is, the learned material can be transferred to different situations (Squire, 2004; Meeter et al., 2008). The neural substrate is proposed to be located in the hippocampus and the medial temporal lobe (Squire, 1992, 2004). The prefrontal lobe and the association cortices also are known to be involved in the explicit memory processes (Cabeza and Nyberg, 2000; Kandel et al., 2000). The memorization and retrieval of the PIN number for your bank account is an output of explicit memory whereas the recall of implicit memory needs a pin pad to acquire the PIN number by the automated finger movements - the performance.

Implicit memory is split into four subcategories associated with different brain areas: the striatum, the neocortex, the amygdala, and the cerebellum. These four brain areas are assigned to the four implicit learning forms: *procedural learning, priming, associative learning, and non-associative learning* (Figure 1). One of the first paradigms used in *priming* was the word-stem completion task which showed a higher preference for completion of word stems with words the participants has been exposed to before without being aware of (Graf et al., 1984). Operant conditioning (i.e. the skinner box) and classical conditioning (i.e. Pavlov conditioning) are subforms of *associative learning*. The two forms of *nonassociative learning* are habituation (decrease of a response to a repeated unimportant stimulus) and sensitization (enhanced response to repeated stimulus). Pro-

cedural learning is the focus of the thesis and will be introduced more detailed in the next paragraph.

Recently, the scheme presented here (Figure 1) was modified in terms of the "strict" assignment of the brain areas to the learning forms. On the one hand, there is the assumption that memory systems are not represented by only one but several brain areas as seen in the corticostriatal loop in habit learning, where basal ganglia and frontal areas are involved similarly in the process of building a habit (Kandel et al., 2000). The habit formation process is disrupted when involved areas are lesioned (Yin and Knowlton, 2006). On the other hand, learning can happen via substitution by other brain areas even when the actual responsible brain areas are lesioned (Packard and McGaugh, 1996).

Procedural learning

This work focuses on the subcategory *procedural learning* which encompasses skill learning (motor, perceptual and cognitive) as well as habit learning (settling a pattern/behaviour following a stimulus) which helps us to deal with the demands of daily life.

Here are several examples on procedural learning:

- learning the mother tongue without effort and without the explicit knowledge about grammar or the like
- response learning, such as following a well-learned route, like the way from home to work
- motor skill learning, the ability to coordinate movements accordingly in daily life as well as for well-practised sports, i.e. tennis, basketball
- expertise, when declarative knowledge gets automatised such as when playing chess
- category learning, i.e. putting objects, humans, or events in learned or self-made categories, e.g. assigning a red sign to the "pay-attention" category which helps one to react (fast) in an appropriate manner

This knowledge is known to be automatic, robust, specific, and inflexible, and requires little attention or cognitive effort during execution. To acquire procedural knowledge, declarative knowledge is not required, but can sometimes enhance learning. Contrarily the attempt to memorize skill or habit learning consciously can disrupt the learning process (Squire, 2004).

Studies on procedural learning in animals are mostly done using motor skill paradigms (skill reaching task, rotarod task). Lesion studies on animals have examined the neural

correlates of procedural learning. In a double dissociation study rats with damage either in the caudate nucleus (located in the striatum) or the hippocampal system (fimbria-fornix in rats, located in the Medial Temporal lobe (MTL)) were tested in a "win-stay-task" (Packard et al., 1989). In this task rats have to learn to visit the arms of the maze which were lighted to receive a reward, and visits to unlit arms were counted as errors. Rats with lesioned caudate nucleus were impaired due to interrupted stimulus-response learning, whereas rats with damage in the fimbria-fornix performed even better than control rats. In the second task - the win-shift task - a pellet was placed in each of the eight arms of the maze, and rats have to learn to collect all 8 pellets without revisiting an arm. Here, caudate-lesioned rats were not impaired whereas fornix-lesioned rats performed worse than controls. This double dissociation study showed that the hippocampal system is crucial to memorize the arms (memorizing events, working memory) where the rat had already been whereas the striatum is necessary to build up habits (stimulus-response).

The most famous human study examining procedural learning without declarative memory is the patient H.M. After removal of his MTL due to severe epilepsy symptoms H.M. suffered from amnesia. This patient still had an intact short-term memory after surgery so he was able to remember facts over seconds or minutes when not distracted, and he had an intact long-term memory from which he was able to retrieve events which had occurred long before the operation. But he could not memorize new facts such as telephone numbers or names longer than a few minutes. However, several cognitive abilities were spared, e.g. he improved in a mirror drawing task without realizing that he had done the task several times before (Gabrieli et al., 1993).

In the last decades a growing body of studies have examined procedural learning in humans. Several experimental tasks have been established such as artificial grammar task (Reber, 1967), in which subjects are instructed to memorize a set of strings of letters following some kind of unbeknown semantic rules. After the memorization phase, new strings of letters are presented, and subjects must classify them to be either semantically correct or incorrect according to the memorized strings. Although participants were not able to verbalize the rules or even to realize that the memorized strings followed any rules, they were able to perform above chance at deciding whether the probe strings were correct or not. Another common task involving motoric components related to skills like writing, is the serial reaction time task (SRT, (Willingham et al., 1989; Nissen and Bullemer, 1987)). Here, participants press buttons following an asterisk that appears on the screen at different positions. The positions where the asterisks appear follow a given sequence. Subjects learned to optimize the speed of their button presses, which was seen in the improvement of their reaction times, whereas the reaction times in the control random sequences did not improve. However, when being asked to retrieve the sequences, the subjects failed to do so. Amnesic patients with lesion in the MTL or diencephalic

area were tested in these tasks (Knowlton and Squire, 1994; Nissen and Bullemer, 1987; Reber and Squire, 1994) and showed similar performance to control subjects suggesting that the MTL is not involved in skill learning.

Using new techniques such as EEG (Electroencephalography), PET (Positron emission tomography), MRI (Magnetic resonance imaging) or TMS, and new analysis methods like Voxel lesion symptom mapping (VLSM (Bates et al., 2003)), neuropsychological studies were complemented to translate the neural substrates associated with procedural learning in animal lesions studies to the human brain.

Motor learning

Motor skill learning culminates in the ability to execute movements fast and accurate without any effort. Being mobile and flexible is one of the most important abilities to feel and be independent - this ability is available for any healthy person. Normally, we can move freely without thinking of the movement itself, be that walking, riding a bicycle, swimming, or even something more trivial like grabbing a glass of water or putting on socks.

Motor skill learning paradigms have often been used to examine learning behaviour and the underlying neural substrates. Motor skills are learned by repeated practice of a complex movement sequence and may be retained for a long time after learning (Sanes, 2003).

Knowledge about the acquisition of motor skills has been acquired through animal studies on rodents and monkeys (Costa et al., 2004; Luft et al., 2004a,b) and in recent years also through human studies using new neuroimaging techniques like fMRI, PET, TMS and transcranial direct current stimulation (Doyon and Ungerleider, 2002; Doyon and Benali, 2005). Motor skill learning involves different stages: a fast learning phase occurring during sessions, a slow learning phase between sessions, and a consolidation period which starts online during training, continues after training, and leads to long-term retention of the skill (Dayan and Cohen, 2011; Luft and Buitrago, 2005). Fast learning increases the activation in the frontal areas of the brain (dorsolateral prefrontal cortex (DLPFC), primary motor cortex (M1) and the anterior portion of the supplementary motor area (preSMA)) and the whole process shifts into the slow learning phase when improvements decelerate to posterior areas i.e. SMA, parietal areas, striatum and cerebellum (Floyer-Lea and Matthews, 2005) with key contributors M1 and striatum (Luft et al., 2004a,b; Wachter et al., 2009). These findings propose a shift from more executive and attentional requirements during the initial phase of learning to an automated habit (Lehéricy et al., 2005; Poldrack et al., 2005; Yin et al., 2004). Grey matter and white matter in brain areas involved in the task during skill learning have been shown to increase in volume (Draganski et al., 2004; Boyke et al., 2008). Injection of protein synthesis inhibitors (Anisomycin) in

to M1 (Luft et al., 2004a,b) and the striatum (Wächter et al., 2010) as well as lesions in these areas (Schubring-Giese et al., 2007) showed an impaired learning performance in rodents.

Stroke survivors often suffer from hemiparesis. Paresis of the lower extremities impairs locomotion. Immobility causes dependency, depression (Dafer et al., 2008), and reduces cardiorespiratory fitness leading to a higher cardiovascular risk (Hooker et al., 2008). Conventional therapy forms are commonly accepted and applied in stroke rehabilitation; however, these therapies are mainly limited to the subacute stage and aim only to restore basic movement function but do not take into account the knowledge gained from experimental (e.g. neuroplasticity) and clinical neurosciences (e.g. pharmacological treatments paired with exercise training). Recently, new approaches have been invented to render the therapy of stroke patients (and other injured patients) more effective and customisable to every individual patient. The plasticity of the brain mentioned above has interesting repercussions for several approaches to rehabilitate the stroke survivor. Besides molecular biological approaches (chemical agents to modulate growing of neural substrate, providing precursor cells) and in vivo electrical stimulation (i.e. TMS) a number of exercise approaches inspired by insights into learning mechanisms have been invented. Robot aided therapy forms use a combination of force and feedback of the movement. CIMT for the upper limb force the patient to use the weaker limb by restraining the healthy side (Dobkin, 2004). Although these therapy forms showed benefits for stroke patients even long after stroke onset, they are still not integrated into clinical routine. The therapy response of individual patients is highly variable. It is therefore necessary to identify the parameters that predict the benefit of individual therapies. Only when these predictors are detected and custom therapies can be prescribed, the incentive for the next step is set, i.e. develop these therapies to reduce the financial and man-force costs so that they are accessible for the majority of patients and are included within the "'conventional"' rehabilitation program.

Treadmill aerobic exercise (TAEX) training involves many characteristics of a skill learning task: repetitive movements, adaptation to individuals, and somatosensory feedback - these characteristics were shown to be crucial for motor learning. TAEX is a rehabilitation approach for stroke survivors to relearn or improve walking and additionally gain cardiovascular fitness. Studies with TAEX varied in intensity and duration of the therapy. A previous review about treadmill training with and without body weight support found no significant effect in stroke survivors (Moseley et al., 2005). However, only one trial exposed their patients with a longer continuous training period (> six weeks) and also training intensity was quite low for most of the studies (Moseley et al., 2005).

It has been shown for other motor skill tasks that the learning effect is most prominent

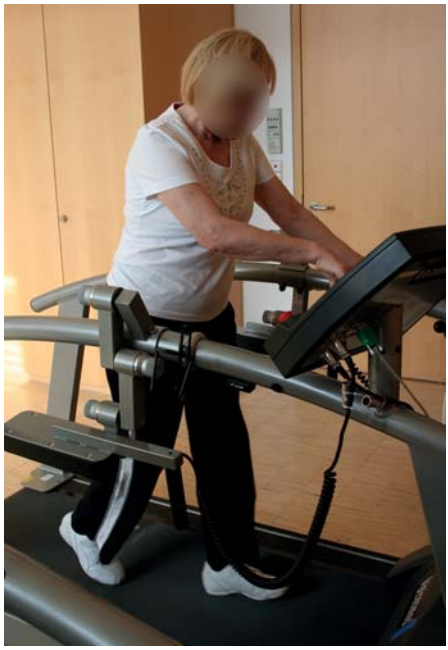

Figure 2. *Treadmill training with railing support.*
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when training sessions are repeated often and when the interval between sessions was selected carefully (Shea et al., 2000; Lee and Genovese, 1989). Several recent studies adjusted the TAEX training: they applied a progressive higher intensity on the training and also prolonged the training period (Luft et al., 2008; Ivey et al., 2008; Macko et al., 2005). Stroke survivors with a stroke longer than six months ago (the time point when spontaneous recovery is assumed to be finished and reached the so called "'plateau"' (Jørgensen et al., 1995)) performing progressive TAEX training have improved cardiovascular fitness (i.e. measured VO_2 peak increased significantly after training) and functional walking ability (Macko et al., 2005). The benefits of TAEX training have been suggested to be mediated by brain plasticity. Luft et al. (2008) tested the brain activity of patients who underwent a progressive TAEX training within 2 weeks of the start and end of the training using fMRI and showed that the contralesional side of the subcortical-cortical network is more activated after training. The brain hemisphere controlling the non-paretic limb did not show any brain adaptations. Recently TAEX training with and without body-weight support to improve gait pattern and cardiovascular fitness has been used to complete conventional occupy therapies (Raine, 2009).

Although TAEX has been shown to be effective and to change the brain activation following improvements in gait and fitness, the therapy response of individual patients seems to be varied and inhomogeneous over all studies using TAEX. Therefore an important goal is to detect the parameters which influence the benefit of TAEX training in stroke rehabilitation. Certainly, the baseline function of gait, fitness, and also the motivation of the individual patients all play a crucial role when customizing the training plan. In patients with upper limb hemiparesis it has been shown that changes of the motor map depends on the lesion location (Luft et al., 2004d). In the first publication "Predictors of Response to Treadmill Exercise in Stroke Survivors" I examined whether clinical factors and lesion location are influential predictors for the amount of therapy gain in TAEX training.

Category and reward learning

Category learning is a highly important ability of any organism. On a daily basis we are exposed to massive amounts of sensory inputs which need to be filtered and carefully selected to derive actions. With this ability one is able to differentiate between "good and bad", e.g. food or poison, between friend or foe, etc. Category learning has previously investigated in animal studies, neuropsychological studies, neuroimaging studies, and using theoretical approaches (Kéri, 2003).

Categorization paradigms vary, and different brain regions are involved when subjects perform them. The unstructured categorization task, rule-based tasks, the prototype distortion tasks and the information integration tasks has been used to study category learning (Ashby and O'Brien, 2005; Ashby and Maddox, 2005; Kéri, 2003). While the unstructured categorization task (Ashby and O'Brien, 2005) and rule-based tasks (Ashby and O'Brien, 2005; Kéri, 2003; Kimberg et al., 1997; Lombardi et al., 1999; Ashby and Maddox, 2011) rely on the explicit memory, and the prototype distortion tasks is based on the perceptual representation system (Reber et al., 1998; Reber and Squire, 1999; Seger et al., 2000), the information-integration tasks are suggested to be based on procedural learning.

In information-integration tasks participants need many repetitions and learn the task slowly. The information of exemplars seen before has to be integrated before a decision for one category is made (Ashby and Maddox, 2005). The SRT task is a commonly used paradigm testing procedural learning. Here, participants learn a sequence of finger tapping by following a sign on a screen. Learning is measured by the decrease of reaction time (Willingham et al., 1989). This task is proposed to be learned implicitly as participants fail to generate the sequence explicitly (recall) although their performance shows a learning effect by reduced reaction time. Also changing the response location interferes with the performance but not changing the finger movements (switching the hands

on the keyboard) (Willingham et al., 2000; Ashby et al., 2003). However, when training progresses it has been shown that participants are able to generate at least the first few items of the sequence explicitly (Ashby and Maddox, 2005). Neuropsychological studies (e.g. Filoteo et al., 2005) showed that more complex information integration tasks (i.e. nonlinearly separable categories whose rules are highly complex) cannot be learned by patients with PD, suggesting a crucial role for the striatum in information integration task - at least in the more complicated forms.

Another important characteristic of category learning is the differentiation between the deterministic and probabilistic nature of the category association (Ashby and Maddox, 2005; Seger and Cincotta, 2005). A paradigm commonly used to test procedural learning is based on probabilistic association between cue and outcome (Knowlton et al., 1996; Poldrack et al., 2001; Fera et al., 2005). In the original version of the task participants had to predict the weather depending on a combination of 4 tarot cards. In a categorization task with probabilistic associations the performance cannot be as optimal as in a category task with exemplars which are clearly a member of a category.

Among several variables like switching the response location (switching keys in SRT (Ashby et al., 2003)), providing feedback also seems to play a crucial role in information-integration tasks. Whereas rule-based learning (relying on explicit memory systems) and to some extend prototype-distortion learning can happen without feedback, it has been shown that information integration learning depends on feedback (Ashby et al., 2002): Rule based learning is not interrupted by a feedback delay more than 10s whereas performance in information-integration learning is severely impaired by a feedback delay of 2.5s (Maddox and Ing, 2005). Neuroimaging studies have shown that activation in the caudate nucleus which has been suggested to play an important role in feedback/reward processing increases in the beginning of learning and decreases when learning progresses (Seger and Cincotta, 2005). However, Poldrack et al. (2001) showed in a fMRI study in young healthy participants that in feedback learning the medial temporal lobe is active in the very beginning of learning whereas the caudate is inactive, but rapidly this activation reverses and the activation in the caudate increases with learning. The early activation of the MTL is suggested to be due to development of representation of new stimuli. After representation is stabilized, the activation in the MTL decreases. Apart from these brain areas a meta-analysis by Liu et al. (2011) on reward processing showed a higher activation for the Nucleus accumbens (NAcc) and the posterior cingulate cortex when processing positive feedback compared to negative feedback.

In this work, I used the weather prediction task (Knowlton et al., 1996) to examine learning performance in healthy elderly and stroke patients, the influence of feedback, and the related brain areas. In this task four cards with geometric forms (circles, diamonds,

squares, triangles; Figure 3) are used to build up 14 combinations. A combination can involve one, two or three cards. These combinations are associated with two categories (sun or rain) in a probabilistic manner. The probabilistic character is to keep the participants unsure about the association. The WPT is a two-alternative forced choice task: participants have to press category A (sun) or category B (rain) after a card combination is presented. The actual weather outcome is determined by a probabilistic rule based on the probabilities of each individual card. Feedback is provided in the form of a smiley face or a frowney face together with the words ”right” or ”wrong” appearing on the screen after the button press. In that way, participants need to learn incrementally trial by trial the optimal stimulus - outcome association. In the analysis, trials in which participants press for the category with the higher probability (>50%) are counted as correct choices, even if a frowney face appeared on the screen as feedback. In previous studies it has been shown that participants reach above chance performance even if they reported not to recognize any relation between combinations and outcomes (Knowlton et al., 1996).

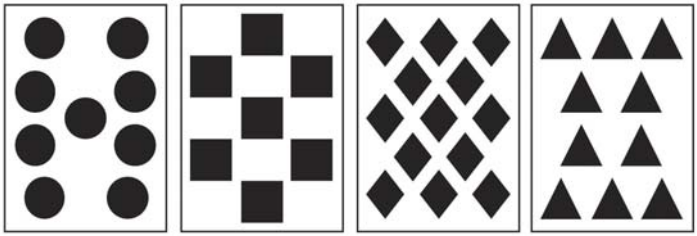

Figure 3. *Cards used in the weather prediction task (WPT).*

Knowlton et al. (1994) showed that the performance on WPT of amnesic patients who had a lesion in the MTL was similar to control subjects' performance at least for the first 50 trials; however, control subjects' performance improved with more trials, whereas amnesic patients stayed on the same level. In another study using the method of double dissociation, the WPT was tested in both amnesic patients with damage in the MTL and patients with Parkinson Disease (PD, Figure 4,(Knowlton et al., 1996)). In this double dissociation study amnesic patients performed as well as controls, whereas patients with PD failed to reach significant above-chance performance - this was even more prominent for the severely affected patients (PD*). When extending the training trials PD patients showed a trend of improvement which might have resulted from the development of explicit knowledge after extensive training. Patients with PD showed similar learning as controls in another study (Moody et al., 2004) which could be due to milder form of PD the patients had (measured with the Hoehn and Yahr Stage). More interesting is the different brain activation in patients and controls, who showed a fronto-striatal activation involving the frontal cortex, the occipital cortex, and the basal ganglia (BG, putamen and caudate nucleus) whereas patients with PD who demonstrate some learning effect showed brain

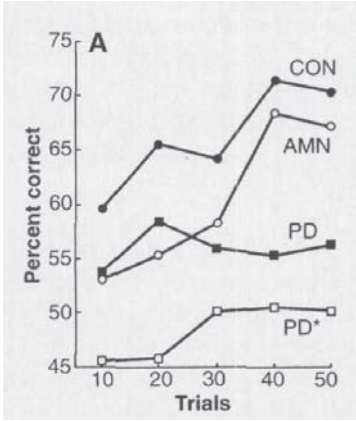

Figure 4. *Performance of healthy control participants, amnesic patients and patients with PD. The performance of control participants and amnesic patients show a sigmoid learning curve reaching a plateau at 65-70% after trials, whereas PD patients are impaired at this task and particular severe PD cases (PD*) show even worse performance. From Knowlton et al. (1996).*

activation in the frontal area and the hippocampus (Poldrack et al., 1999; Moody et al., 2004). These results suggest that the weather prediction task can be solved with simple strategies such as explicitly memorizing single trial patterns, but to reach higher performance it is necessary to use the frontostriatal circuits (Gluck et al., 2002). Using fMRI with young healthy individuals, Poldrack et al. (2001) showed the existence of an interaction between brain areas MTL and BG, involved in the WPT. First they showed that the brain activation of the MTL and the caudate nucleus were negatively correlated when comparing the feedback based task (WPT) and the pair associated task (PA), in which only card combinations paired with the outcome sun or rain must be memorized. The caudate nucleus was activated more during the WPT whereas the MTL showed higher activation during the PA task. This result also supports the assumption that the caudate nucleus is involved in feedback processing. Furthermore Poldrack and colleagues showed a reciprocal activation change of MTL and BG during the performance of the WPT. Early in learning the MTL was activated (when BG activation was low) which might reflect its crucial role during initial stimulus presentation. Later in learning the activation of the MTL decreased and at the same time the activation of the BG increased, suggesting that the task got more habit-like. These findings suggest an interaction between the explicit memory system and the implicit memory system.

To date the number of studies on procedural learning tasks with stroke patients are small. Using two different implicit motor learning tasks, Boyd et al. (2007) and colleagues showed that the severity of stroke impacts the performance of patients in both tasks. However, mild and moderate stroke patients showed different behaviours related to the two tasks: the control group and the mild stroke group showed different reaction time changes between the two tasks whereas the moderate stroke group's performance did not show any difference between tasks. This is an important finding when comparing re-

sults of studies. Another study showed an improvement in learning the serial reaction time task in chronic stroke patients when administered with levodopa compared to placebo patients (Rösser et al., 2008). Bellebaum et al. (2008) showed that stroke patients with focal BG damage performed an implicit reward learning task at performance levels comparable to the control sample. However when the associations of symbol and outcome were reversed, patients' performance deteriorate. This deterioration has been suggested to result either from deficient processing of negative feedback or from the inability to transfer knowledge.

While my first publication addresses the influence of clinical factors and lesion location in motor learning, the second publication "Predictive value and reward in implicit classification learning" and the third publication "Impaired reinforcement learning after stroke" follow up on further possible influential parameters with a focus on the process of feedback in procedural learning.

Aim of the thesis

To improve the motor function after stroke is of high clinical interest. Studies on new rehabilitation approaches such as treadmill aerobic exercise training show improvements of motor disability in chronic stroke patients, although the variability in benefit is quite large (Macko et al., 2005; Luft et al., 2008). The objective of my thesis is to identify influential parameters which explain the variability of therapy effects.

In the first study ("Predictors of response to treadmill exercise in stroke survivors") we pooled the data of two clinical treadmill exercise trials with stroke survivors to examine the predictors of effect of this training on walking ability (which for stroke survivors is learning of a new skill or making a residual skill more automatic and less attentive) and cardiorespiratory fitness. Factors such as baseline gait functions, age, lesion location, lesion volume, NIHSS score, and stroke-therapy interval were included as potential predictors.

Clinical parameters could only explain one third of the variability of therapy effects. Therefore we aim to find further parameters which could in the future help to explain the response variability and, in a next step, to assign patients to promising therapies. Reorganization and plasticity of the brain seem to play a crucial role during learning processes as well as during rehabilitation processes (Luft et al., 2008; Dayan and Cohen, 2011; Fera et al., 2005). Therefore principles in procedural learning could be transferred to rehabilitation processes. Previous studies on procedural learning have shown that reward and feedback provision influence learning performance (Ashby et al., 2002; Maddox and Ing, 2005) and activate brain areas such as the basal ganglia, and the prefrontal cortex.

We used a probabilistic categorization task, the weather prediction task to test our hypothesis that learning performance in stroke patients is impaired due to malfunction of the reward system. Whether the valence of provided feedback and the valence of the content to be learned in implicit learning plays a crucial role and which brain areas are involved in this process are the main focuses of the second and the third fMRI studies on healthy seniors ("Predictive value and reward in implicit classification learning") and stroke survivors ("Impaired reinforcement learning after stroke").

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Publications & Manuscripts

Predictors of Response to Treadmill Exercise in Stroke Survivors

Aims of this study, main findings, and own contributions

Stroke survivors often have to struggle with their overall disability. Several therapies for gait improvement have been examined in randomized controlled trials (Luft et al., 2008; Ivey et al., 2008; Macko et al., 2005). Positive group effects have been shown for treadmill training (Macko et al., 2005) even years after the index stroke. However, little is known about the parameters determining individual response to therapy. Knowing the parameters which influence the rehabilitative benefit of the therapies can help in the selection of therapies and to optimize treatment protocols.
In this study, we pooled two samples of stroke patients who completed a treadmill training. Treadmill aerobic exercises (TAEX) retrain cardiorespiratoray fitness as well as improve the gait performance. Patients completed a TAEX training over 6 months (US) or 3 months (Germany trial). Before and after the training period patients were tested on gait parameters (10m walk and 6minutes walk) and fitness parameters (peak VO_2 [(ml/kg bodyweight)/min]). Other parameters such as age, time since stroke, NIHSS, lesion size, and location have been collected as well. Cardiorespiratory fitness and gait assessments improved after training; however no correlation between these two parameters could be observed. Patients with smaller, subcortical, left-sided lesions showed the largest benefit of walking. The shorter the time since stroke, the greater the benefit. Predictors explained 33% of the variability in therapy effects.

This study was published in Neurorehabilitation & Neural Repair in 2010 as
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Delineation of author contributions:

- I (JML), CG, JC tested the participants of the Germany trial.
- I (JML) and CG analysed the datasets of the Germany and the US trial and wrote the manuscript.
- BH analysed part of the datasets of the US trial.
- KU provided support for MR experiments in the Germany trial.
- ARL, LWF, RFM and DFH designed the study.
- CB reviewed the manuscript.
- ARL wrote/reviewed the manuscript as supervising author.

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Predictors of Response to Treadmill Exercise in Stroke Survivors

Judith M. Lam[1,2], Christoph Globas, MD[3], Joachim Cerny[3], Benjamin Hertler[1], Kamil Uludag, PhD[4], Larry W. Forrester, PhD[5,6], Richard F. Macko, MD[5,7], Daniel F. Hanley, MD[5,7], Clemens Becker, MD[3], and Andreas R. Luft, MD[1,6,7]

Abstract

Background. Aerobic treadmill exercise (T-EX) therapy has been shown to benefit walking and cardiorespiratory fitness in stroke survivors with chronic gait impairment even long after their stroke. The response, however, varies between individuals. *Objective*. The purpose of this post hoc analysis of 2 randomized controlled T-EX trials was to identify predictors for therapy response. *Methods*. In all, 52 participants received T-EX for 3 (Germany) or 6 (United States) months. Improvements in overground walking velocity (10 m/6-min walk) and fitness (peak VO_2) were indicators of therapy response. Lesion location and volume were measured on T1-weighted magnetic resonance scans. *Results*. T-EX significantly improved gait and fitness, with gains in 10-m walk tests ranging between +113% and −25% and peak VO_2 between −12% and 88%. Baseline walking impairments or fitness deficits were not predictive of therapy response; 10-m walk velocity improved more in those with subcortical rather than cortical lesions and in patients with smaller lesions. Improvements in 6-minute walk velocity were greater in those with more recent strokes and left-sided lesions. No variable other than training intensity, which was different between trials, predicted fitness gains. *Conclusions*. Despite proving overall effectiveness, the response to T-EX varies markedly between individuals. Whereas intensity of aerobic training seems to be an important predictor of gains in cardiovascular fitness, lesion size and location as well as interval between stroke onset and therapy delivery likely affect therapy response. These findings may be used to guide the timing of training and identify subgroups of patients for whom training modalities could be optimized.

Keywords

stroke, lesion, gait, rehabilitation, aerobic treadmill exercise

Introduction

Impaired gait after hemiparetic stroke contributes strongly to overall disability. Aerobic treadmill exercise (T-EX) has been successfully used to retrain gait and improve cardiorespiratory fitness at the same time, thereby, reducing the disability related to immobility. Several randomized controlled trials have demonstrated benefits on various outcome parameters in patients with chronic gait impairments.[1-4] Although group effects are significant, the individual response to T-EX is variable. The reasons for this variability are not known. Identifying predictors of therapy-related benefits will serve to select and adjust the intervention to the individual patient.

For other rehabilitative treatments, predictive parameters have been reported. Using functional magnetic resonance imaging,[5,6] transcranial magnetic stimulation,[7,8] or positron emission tomography,[9] it was shown that different brain areas undergo lasting changes after stroke and after rehabilitative interventions. These changes in brain activation are associated with the degree to which motor function recovers. Cramer and coworkers[10] suggested that lower baseline motor

[1]University of Zürich, Zürich, Switzerland
[2]Hertie Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany
[3]The Robert-Bosch-Krankenhaus, Klinik für geriatrische Rehabilitation, Stuttgart, Germany
[4]The High-Field Magnetic Resonance Center, MPI for Biological Cybernetics, Tübingen, Germany
[5]University of Maryland, School of Medicine, Baltimore, MD, USA
[6]Johns Hopkins University, Baltimore, MD, USA
[7]Baltimore VA Medical Center Geriatric Research, Education and Clinical Center (GRECC), Baltimore, MD, USA

Corresponding Author:
Andreas R. Luft, Department of Neurology, University of Zürich, Frauenklinikstr 26, 8091 Zürich, Switzerland
Email: andreas.luft@usz.ch

Table 1. Demographic and Baseline Characteristics

	All (n = 52)	United States (n = 20)	Germany (n = 32)	$P_{Difference}$ (US vs German Trials)
Age (years), mean (SEM)	66.8 (1.1)	64.0 (2.1)	68.6 (1.1)	.055
Gender, Female (%)	18 (34.62)	12 (60)	6 (18.75)	.036[a]
Stroke therapy interval (months), mean (SEM)	59.00 (9.28)	60.06 (20.01)	58.34 (8.77)	.93
Stroke location, n (%)				
Brainstem	8 (15.38)	6 (30)	2 (6.24)	
Cortex	20 (38.46)	5 (25)	15 (46.88)	
Subcortical	24 (46.15)	9 (45)	15 (46.88)	
Right-sided stroke, n (%)	20 (38.46)	8 (40)	12 (37.5)	.86
Lesion volume (mm^3 SEM)	37421.54 (8065.83)	45775 (11484.75)	24056 (9717.42)	.16
NIHSS, mean (SEM)	4.08 (0.35)	3.67 (0.53)	4.31 (0.47)	.39

Abbreviations: SEM, standard error of the mean; NIHSS, National Institutes of Health Stroke Scale.
[a]Indicates significant differences between trials ($P < .05$).

cortex activation predicts higher therapeutic benefit. Given that brain activation during hemiparetic movement depends on the location and size of the brain lesion,[6] it is conceivable that lesion geometry has prognostic value. Lesion geometry indeed explains part of the variability in acute deficits after stroke and of functional outcomes at 3 months.[11-15] However, some studies have failed to show such relationships.[10,16]

Age was also identified as a predictor of functional outcome in previous studies.[17,18] This may be explained by higher frequency of comorbidity, stroke-related complications,[14] and limited plasticity of the aging brain.[19] The objective here was to investigate the value of clinical, demographic, and lesion-related variables to predict the benefit provided by T-EX in chronically disabled stroke survivors.

Materials and Methods

Participants

This post hoc analysis combines data from 2 randomized controlled trials that were conducted by the same collaborative group of researchers. In the first trial, they compared 6 months of aerobic T-EX with stretching exercises of equal duration in Baltimore, Maryland.[2,20] In the second trial conducted in Stuttgart, Germany, they compared 3 months of T-EX to conventional care. Here, data for the 52 participants from the T-EX groups of both trials for whom structural imaging data were available are analyzed (Table 1).

Participants in both studies had suffered a first-ever ischemic stroke at least 6 months prior to enrollment. Exclusion criteria were heart failure, unstable angina, peripheral arterial occlusive disease, aphasia, dementia, untreated major depression, clinical and/or neuroimaging signs of stroke-independent neurological diseases (eg, Parkinsonian syndromes), patients already performing aerobic exercise training for >20 min/d and >1 d/wk, and other medical conditions precluding participation in exercise (for details see ACSM[21]). The trials were approved by the institutional review boards of the University of Maryland and the Johns Hopkins University (US trial) and the Ethics Committee of the University of Tübingen, Germany (German trial). All participants provided written informed consent.

Assessments of Gait Function and Cardiovascular Fitness

Participants were enrolled when capable of completing ≥3 consecutive minutes of treadmill walking at ≥0.1 m/s without personal or body weight support (use of hand rails was allowed) and without signs of myocardial ischemia or other contraindications to training. During a peak-effort T-EX test with open-circuit spiroergometry, cardiovascular fitness was determined by measuring VO_2 in (mL/kg body weight)/min according to the standards of the American Heart Association[21,22] under continuous monitoring of vital signs and ECG. For peak VO_2 testing, a modified Balke protocol (increase of treadmill incline every 2 minutes with constant speed) was applied—a procedure to assess cardiovascular fitness in stroke patients with a reliability of repeated measurements of heart rate, systolic blood pressure, oxygen consumption (VO_2 in L/min), VO_2 (mL/kg/min), respiratory exchange ratio, rate pressure product, and oxygen pulse.[23] Locomotor impairments were assessed by 2 widely used and well-characterized tests.[24,25] The time required to walk 10 m at fastest and comfortable paces was used to assess the ability to walk short distances typical for the home environment. The distance walked during 6 minutes was added to evaluate sustained walking capacity. To render both tests comparable to each other and to published reference data, the mean velocity was

calculated for both walking tests and was used in further analyses. Functional assessments were conducted before and after the training period.

Training

The T-EX training goal was three 40-minute exercise sessions per week at an aerobic intensity of 60% in the US trial and 80% of heart rate reserve (HRR) in the German trial. Duration and intensity started at low values (10-20 minutes, 40%-50% HRR) and increased by approximately 5 minutes and 5% HRR. To reach the training intensity target, treadmill velocity was increased by 0.05 m/s every 1 to 2 weeks as tolerated. In the US trial, training was conducted for 6 months and in the German trial, for 3 months.

MRI Data Acquisition

In the US trial, structural MRI data were collected using a 1.5 T Philips scanner (Philips, Eindhoven, Netherlands) within 2 weeks of the start and end of the training. In the German trial, MRI data were acquired from a 3T scanner (Vision, Siemens, Erlangen, Germany). T1-weighted images (3D-MPRAGE sequence, resolution 1 mm^3) covering the entire brain were acquired to determine lesion location and size. Functional MRI data collected in the US trial are reported elsewhere.[2]

Image Analysis

Lesion location was first determined by visual inspection performed by 2 raters independently (ARL and BH for the US trial; JML and CG for the German trial). Lesions were stratified into cortical/subcortical white matter with or without basal ganglia involvement, referred to as *cortical* lesions and *subcortical* lesions. The latter were defined as lesions restricted to the region medial to the insula and inferior to the corpus callosum. Brainstem lesions were regarded as subcortical.

To determine lesion volume, binary lesion masks were produced by manually segmenting the lesion area on all consecutive sections displaying the lesion. Lesion area was defined on T1 images as all voxels isointense to CSF plus hypodense voxels at the boundary of the lesion core. Manual segmentation was performed using MRIcro.[26] All voxels defining the lesion (1 voxel = 1 mm^3) were counted using a Matlab script.

Statistical Analysis

The changes in functional assessments (10-m walk test, 6-minute walk test, and peak VO_2) were expressed as absolute change and change relative to baseline performance. Relative changes were analyzed because we expected patients with more impairment to show less absolute improvement as compared with patients with smaller deficits. General linear models were used to assess the effects of age, gender, stroke-onset to therapy-onset interval, and lesion volume, side, and location (cortical, subcortical) on the dependent variables. Dependent variables were either baseline performance or change of performance (absolute or relative to baseline) in fitness and walking tests. In the models investigating change variables, the baseline value of the respective change variable was added as a covariate. Independent variables were entered into the model in a stepwise fashion using a criterion of $P < .25$ and then removed if $P > .05$. After identifying significant predictors, 2-way interactions between them were first added to the model and then removed if their effect was insignificant ($P < .05$). The efficacy of T-EX to improve fitness and gait was tested using repeated-measures ANOVA models, one for each outcome parameter. All data are expressed as mean ± standard error of the mean.

Results

Baseline Functional Impairment

The patients enrolled in Germany walked faster at their self-selected pace at baseline and had better cardiovascular fitness (Table 2) compared with those in the US trial. Overground walking velocity as measured in the 6-minute walk test and velocity in the 10-m walk test was slower in women, in older participants, in those with larger lesions (for the 10-m walk test fastest pace), and at higher baseline NIHSS score (Table 3). For gait velocity derived from the 6-minute walk test, we found a higher negative correlation with NIHSS score among participants in the German trial than in the US trial. Low cardiorespiratory fitness was predicted by female gender, right-sided lesion, and high (indicating greater impairment) NIHSS score. No other interactions between trial and other independent variables were significant.

Exercise-Related Functional Gains

Treadmill training led to increased gait velocity as measured by the 10-m walk test (fastest pace 0.85 ± 0.06 to 0.96 ± 0.06 m/s, $P < .0001$; comfortable pace 0.67 ± 0.05 to 0.75 ± 0.05 m/s, $P = .0006$) and as measured during the 6-minute walk (0.70 ± 0.05 to 0.84 ± 0.06 m/s, $P < .0001$). T-EX also improved cardiorespiratory fitness (peak VO_2 17.9 0.94 to 21.7 ± 1.18 mL/kg/min, $P < .0001$). There were no significant correlations between gains in fitness and velocity ($P > .5$ for all gait tests). Absolute and relative gains in these outcome parameters are presented in Table 2.

Predictors of Exercise-Related Functional Gains

Relative improvements in 10-m walk velocities were higher in participants with smaller lesions (Table 3). Relative gains

Table 2. Baseline and Absolute (absCh) and Relative Changes (relCh) in Gait Performance and Fitness

	All (n = 52)			United States (n = 20)			Germany (n = 32)		
	Baseline	absCh	relCh	Baseline	absCh	relCh	Baseline	absCh	relCh
6-Minute walk velocity (m/s), mean (SEM)	0.704 (0.054)	0.127 (0.015)	0.198 (0.023)	0.585 (0.061)	0.115 (0.024)	0.206 (0.046)	0.778 (0.077)	0.135 (0.019)	0.194 (0.024)
6-Minute walk distance (m), mean (SEM)	253.25 (19.38)	45.90 (5.31)		210.6 (21.82)	41.35 (8.65)		279.91 (27.61)	48.75 (6.79)	
10-m Walk velocity (m/s), SSWS, mean (SEM)	0.672 (0.048)	0.059 (0.015)	0.133 (0.035)	0.558[a] (0.057)	0.075 (0.030)	0.217 (0.083)	0.739[a] (0.067)	0.0499 (0.017)	0.083 (0.024)
10-m Walk velocity (m/s), FCWS, mean (SEM)	0.852 (0.063)	0.100 (0.019)	0.156 (0.035)	0.748 (0.083)	0.126 (0.036)	0.25 (0.084)	0.914 (0.087)	0.084 (0.019)	0.100 (0.022)
Peak VO_2 (mL/kg/min), mean (SEM)	17.856 (0.944)	3.957 (0.527)	0.232 (0.030)	14.125[a] (1.214)	2.089[a] (0.510)	0.161 (0.039)	20.188[a] (1.167)	5.066[a] (0.720)	0.274 (0.041)

Abbreviations: SEM, standard error of the mean; SSWS, self-selected walking speed; FCWS, fast comfortable walking speed.
[a]Indicates significant differences between trials ($P < .05$).

Table 3. Predictors of Baseline Walking Impairment and Fitness

Dependent Variable	Predictors	Mean	SEM	*r*	*P*
10-m Walk velocity (m/s), comfortable	Trial (United States)	0.56	0.06		.009
	Trial (Germany)	0.74	0.07		
	NIHSS			−0.54	<.0001
10-m Walk velocity (m/s), fastest	Trial (United States)	0.75	0.09		.036
	Trial (Germany)	0.91	0.09		
	Gender (female)	0.69	0.07		.032
	Gender (male)	0.93	0.08		
	Age			−0.1	.012
	Lesion volume			−0.4	.023
	NIHSS			−0.5	.005
6-Minute walk velocity (m/s)	Gender (female)	0.56	0.06		.009
	Gender (male)	0.77	0.07		
	NIHSS (United States)			−0.14	<.0001
	NIHSS (Germany)			−0.69	
Peak VO_2 (mL/kg/min)	Trial (United States)	14.1	1.21		.013
	Trial (Germany)	20.2	1.17		
	Gender (female)	13.2	1.2		.0004
	Gender (male)	20.3	1.1		
	Stroke side (left)	19.7	1.2		.009
	Stroke side (right)	14.9	1.4		
	NIHSS			−0.28	.003

Abbreviations: SEM, standard error of the mean; NIHSS, National Institutes of Health Stroke Scale.

in 6-minute walk velocity were higher in participants with more recent stroke events. Relative improvement in fitness (peak VO_2) was higher in German than in US participants (Table 3).

Absolute changes in walking or fitness were not predicted by baseline walking velocities or fitness. Absolute improvement in gait velocity measured during the 10-m walk test (fastest or comfortable pace) was greater in participants with subcortical than with cortical lesions (Table 4). Whereas improvements in patients with subcortical lesions were significant for both comfortable and fastest walking velocity (fastest pace: gain = 0.13 ± 0.02 m/s, $P < .0001$; comfortable pace: gain = 0.09 ± 0.02 m/s, $P < .0001$), gains in participants with cortical lesions failed to reach significance (fastest pace: gain = 0.05 ± 0.03 m/s, $P = .08$; comfortable pace: gain = 0.02 ± 0.02 m/s, $P = .5$). Participants with shorter stroke–therapy intervals and left-sided lesions showed greater improvement in 6-minute walk velocity (Table 4, Figure 1). Nevertheless, both left- and right-hemisphere-lesioned participants walked faster in the 6-minute walk test (left-hemisphere lesion: gain in velocity = 0.16 ± 0.02 m/s, $P < .0001$; right-hemisphere lesion: gain = 0.08 ± 0.02 m/s, $P < .001$). Predictive models explained between 10% and 33% of the variability in therapy response (r^2 values, Table 4).

Discussion

This post hoc analysis of 2 trials on aerobic T-EX demonstrates that despite overall significant benefits, the response to T-EX varies between individuals. Predictors of greater benefit in walking parameters were subcortical and left-sided lesion location, smaller lesions, and shorter interval time between stroke onset and onset of treadmill training.

Previous studies have demonstrated a relationship between lesion location and size and stroke-related deficits or benefits of conventional rehabilitation.[11,12,14,15,27,28] Whereas in laboratory animals lesion volume predicts functional deficits,[27,29,30] findings are heterogeneous in humans. Saunders and colleagues[15] reported that for middle cerebral artery (MCA) territory infarctions, lesion volume is a prognostic outcome indicator. Other studies failed to show this relationship.[16,31] Chen et al[12] reported critical lesion sizes for different brain areas: motor impairment was high when lesions were larger than 75 cm^3 for the cortex, 4 cm^3 for the corona radiata, 0.75 cm^3 for the internal capsule, 22 cm^3 for the putamen, and 12 cm^3 for the thalamus. This indicates that functional outcome depends not only on lesion size but also on a combination of lesion size and location. Dawes and coworkers[31] reported a trend for a correlation between corticospinal tract lesion volume and walking performance after a partial body weight support treadmill training. Beloosesky and coworkers[11] reported a correlation between lesion size and rehabilitation success for cortical infarcts. In our data set, lesion volume was an independent predictor in relative gains in 10-m walk gait velocity (independent of baseline deficit). For absolute improvement, lesion location (subcortical vs cortical) was an independent predictor, representing the same association as the association between lesion volume and relative gain

Table 4. Predictors of Therapy Response

Dependent Variable	Predictors	Mean	SEM	*r*	*P*	$r^2_{overall}$
Absolute gain in 10-m walk velocity (m/s), comfortable	Location (cortical)	0.015	0.021		.014	0.12
	Location (subcortical)	0.091	0.020			
Relative gain in 10-m walk velocity (m/s), comfortable	Lesion volume			−0.24	.0023	0.32
Absolute gain in 10-m walk velocity (m/s), fastest	Location (cortical)	0.047	0.025		.018	0.11
	Location (subcortical)	0.134	0.023			
Relative gain in 10-m walk velocity (m/s), fastest	Lesion volume			−0.24	.0035	0.27
Absolute gain in 6-minute walk velocity (m/s)	Stroke side (left)	0.16	0.02		.035	0.33
	Stroke side (right)	0.08	0.02			
	Stroke–Therapy interval			−0.36	.0088	
Relative gain in 6-minute walk velocity (m/s)	Stroke–Therapy interval			−0.31	.017	0.1
Absolute gain in peak VO_2 (mL/kg/min)	Trial (United States)	2.09	0.51		.005	0.15
	Trial (Germany)	5.07	0.72			
Relative gain in peak VO_2 (mL/kg/min)	Trial (United States)	0.16	0.04		.0312	0.15
	Trial (Germany)	0.27	0.04			

Abbreviations: SEM, standard error of the mean.

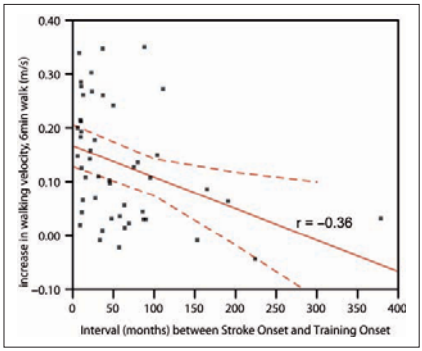

Figure 1. The absolute improvement in 6-minute walk velocity after treadmill exercise is greater in participants who were trained earlier after the stroke

because cortical strokes were substantially larger then subcortical strokes. Whereas patients with subcortical strokes showed significant improvements in the 10-m walk, patients with cortical strokes failed to achieve significant effects. We also found an association between improvement in gait velocity during the 6-minute walk (absolute gain) and lesioned hemisphere. Participants with left-sided lesions improved twice as much in gait velocity as those with right-sided ones; however, both subgroups benefited significantly. Although it has been shown that overall stroke outcomes at 3 months poststroke (modified Rankin scale) were similar for those with left- and right-sided lesions,[32] locomotion was reported to recover better in patients with recent (mean 52 days) left-hemisphere lesions using conventional rehabilitation techniques.[33] This difference may be related to the fact that visuospatial or attention deficits are more prominent in participants with right-hemisphere infarction, and this could interfere with locomotion because these cognitive functions are required for locomotion.[34] It is plausible that 6-minute walks have higher cognitive demands, for example, higher demands for navigation in space, than 10-m walks and might, therefore, be more sensitive to right-hemisphere damage.

Age has been reported to predict poor response to constraint-induced movement therapy,[35] but age was unrelated to the benefits conveyed by treadmill therapy here. Similarly, Luk and coworkers[36] found in 878 stroke survivors that, if corrected for disability before the stroke, age per se does not predict functional independence at the time of discharge from the rehabilitation hospital. In the healthy elderly population, King and coworkers[37] report younger age and better health and physical function at baseline to be predictors of exercise benefits. The reason for not observing predictive effects of age here, especially on fitness gains, may be the smaller age span and younger mean age in our participant sample as compared with those in the study by King et al.

A longer time interval between stroke onset and beginning of treadmill therapy were associated with less improvement in gait velocity measured during the 6-minute walk (absolute and relative). It is noteworthy that this relationship does not reflect differences in the efficacy of interventions delivered in the acute versus the chronic period after stroke because both trials recruited chronic participants at more than 6 months

after their stroke. Although it does not qualify the finding that training on a treadmill can improve walking even long after stroke, this observation stresses the need for continued rehabilitation beyond the commonly prescribed 3 to 6 weeks.

It has been reported that apart from lesion-related parameters, more severe neurological deficits predicted less improvement after therapy for the recovery of arm function.[38] A similar finding was reported for constraint-induced movement therapy.[20] Here, we did not find an association between baseline deficits and therapy response—that is, there was no effect of a baseline functional measure on its absolute change after therapy. However, certain predictors of response also predicted baseline function—that is, lesion volume for the 10-m walk velocity. Their predictive value may therefore be explained via their effect on baseline function. Participants in the German trial had higher fitness levels at baseline than US participants and showed greater improvements, but baseline fitness itself did not predict gains in fitness in the combined study sample. Thus, the effects on fitness gains are not likely to be explained by the differences in baseline values between trials, particularly as one would expect even greater benefits in an unfit patient. The effects could, however, be explained by higher training intensity in the German trial (mean HRR at the end of training was 76% for Germany and 58% for the United States). Apart from that, none of the investigated independent variables (age, gender, baseline walking, stroke–therapy interval, and lesion volume, side, and location [cortical, subcortical]) seemed to predict gains in cardiovascular fitness in the combined sample.

Despite identifying significant predictors here, predictive models explained at most 33% (for 6-minute walk velocity) of the variability in therapy effects. Other parameters, such as the degree of microvascular encephalopathy, brain atrophy, or mental factors such as motivation and ambition to achieve the training goals, were not evaluated here but may be important for predicting the response to T-EX.

The limitation of this study is the combination of 2 trials that were conducted in different populations and used different durations and intensities of T-EX. Because it is difficult to recruit large numbers of chronically disabled stroke survivors for prolonged training within a research study, we decided to pool the data despite these design differences. Trial (the United States, Germany) was a covariate in all analyses, and interaction terms were tested to identify differences between the data sets. As discussed above, the effect of trial was significant only in models predicting fitness gains. This may have been a confounder precluding an identification of predictors of fitness gains.

Conclusion

In summary, the present study provides further support for the efficacy of aerobic treadmill training in chronic stroke survivors. Walking benefits might be related to lesion characteristics, with participants with large and right-sided lesions improving the least. Additionally, earlier intervention after the stroke may optimize treatment effects. These findings might be important to consider when prescribing exercise interventions after stroke but require further confirmation by randomized controlled trials.

Authors' Note

JML and CG contributed equally to this work.

Declaration of Conflicting Interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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Predictive value and reward in implicit classification learning

Aims of this study, main findings, and own contributions

Skill learning is crucial to cope with daily life. Behaviour which is performed regularly can become automated (conversion to a skill) and therefore free capacity in working memory for other more demanding activities. The process of skill learning depends on the emotional situation (Cahill and McGaugh, 1996) and is known to be more effective when feedback is provided.
Here, we used the weather prediction task, an established paradigm to test whether feedback and valence of learned content plays a crucial role in procedural learning. 30 senior adults were tested behaviourally, and those who were eligible and agreed underwent a fMRI scan while performing the task. Participants practised outside the scanner with a short training phase using neutral faces to avoid learning.
Learning was better for card combinations leading to smileys than for those leading to frowneys. In the feedback period smileys showed higher activation in bilateral nucleus accumbens (NAcc), bilateral posterior cingulum, left primary cortex, right postcentral gyrus, and right premotor cortex. Higher activation in the NAcc and the posterior cingulum has been related to reward processing and in particular positive reward in several studies before.
Learning performance was better for the content sun (positive valence) and card combinations that occurred frequently and had a higher predictive value. Brain activation for higher predictive value has been observed in the right cerebellum. An interaction young >old x smiley >frowney activated the left cingulate gyrus, the medial frontal gyrus, and the putamen.

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Delineation of author contributions:

- I (JML) and ARL designed the study.
- I (JML) and ARL performed the data analysis
- I (JML), TW and CG tested the participants.
- I (JML) and TW wrote the manuscript.
- HOK reviewed the manuscript.
- ARL wrote/reviewed the manuscript as supervising author.

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Predictive Value and Reward in Implicit Classification Learning

Judith M. Lam,[1,2] Tobias Wächter,[2,3] Christoph Globas,[1,4] Hans-Otto Karnath,[5] and Andreas R. Luft[1]*

[1]*Clinical Neurorehabilitation, Department of Neurology, University of Zürich and Rehabilitation Initiative and Technology Center of Zürich (RITZ), Zürich, Switzerland*
[2]*Center of Neurology and Hertie Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany*
[3]*German Center of Neurodegenerative Diseases (DZNE), Tübingen, Germany*
[4]*Robert-Bosch-Krankenhaus, Klinik für geriatrische Rehabilitation, Stuttgart, Germany*
[5]*Section of Neuropsychology, Center of Neurology, Hertie Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany*

Abstract: Learning efficacy depends on its emotional context. The contents learned and the feedback received during training tinges this context. The objective here was to investigate the influence of content and feedback on the efficacy of implicit learning and to explore using functional imaging how these factors are processed in the brain. Twenty-one participants completed 150 trials of a probabilistic classification task (predicting sun or rain based on combinations of playing cards). Smileys or frowneys were presented as feedback. In 10 of these subjects, the task was performed during functional magnetic resonance imaging. Card combinations predicting sun were remembered better than those predicting rain. Similarly, positive feedback fortified learning more than negative feedback. The presentation of smileys recruited bilateral nucleus accumbens, sensorimotor cortex, and posterior cingulum more than negative feedback did. The higher the predictive value of a card combination, the more activation was found in the lateral cerebellum. Both context and feedback influence implicit classification learning. Similar to motor skill acquisition, positive feedback during classification learning is processed in part within the sensorimotor cortex, potentially reflecting the activation of a dopaminergic projection to motor cortex (Hosp et al., 2011). Activation of the lateral cerebellum during learning of combinations with high predictive value may reflect the formation of an internal model. *Hum Brain Mapp 00:000–000, 2012.* © 2012 Wiley Periodicals, Inc.

Key words: sensorimotor cortex; nucleus accumbens; cerebellum; reward; classification learning; implicit learning; fMRI

INTRODUCTION

Learning depends on the emotional context in which it occurs [Cahill and McGaugh, 1996]. Pleasant cues with positive valence are better remembered than unpleasant ones with negative valence [Ali and Cimino, 1997; Mneimne et al., 2010] and the opposite may be true for directed forgetting [Minnema and Knowlton, 2008].

Judith M. Lam and Tobias Wächter contributed equally to this work.

*Correspondence to: Andreas R. Luft, MD, Department of Neurology, University of Zürich, Frauenklinikstrasse 26, 8091 Zürich, Switzerland. E-mail: andreas.luft@usz.ch

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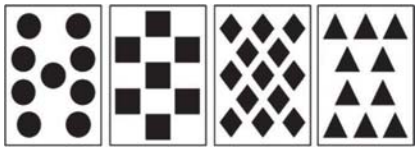

Figure 1.
Set of playing cards. One to three cards were shown to form the card combinations described in Table I.

Feedback in the form of reward or punishment provided during trial-and-error learning also tinges the emotional context. Wächter et al. [2009] showed that implicit motor skill learning is more effective with positive than negative feedback. Brain networks involved in feedback processing include striatum, midbrain, amygdala, frontal, and cingulate cortices; positive and negative feedback are handled by different circuits [Liu et al., 2010].

The hypothesis here was that positive feedback, content of positive valence and high predictive value improve implicit learning and that improved learning is associated with stronger recruitment of brain networks encoding rewards. Because implicit learning mechanisms form the basis of many therapeutic interventions in rehabilitation, it is important to know the effect of these modifiable factors. We recruited subjects from middle to retirement age for a later comparison with individuals after stroke.

We tested our hypothesis using a classification learning paradigm, the weather prediction task [Knowlton et al., 1996], in which subjects had to learn associations between a certain combination of four different playing cards and a dichotomous weather outcome, sun or rain. The associations were stochastic, that is, each combination of cards predicted sun or rain with a certain probability. The subject was supposed to learn which combination predicted which weather. Feedback was given in form of smiley or frowney faces. The stochastic nature limited the subject's awareness of the association. Hence, learning this task was considered to be mainly implicit.

MATERIALS AND METHODS

Subjects and Task

Twenty-one subjects were recruited via advertisements. Participants (14 females, 7 males) were between 43 and 85 years old (mean ± SEM: 64.6 ± 2.1). Inclusion criteria were mini mental state (MMS) ≥27 points and Beck's depression index (BDI) ≤11 points. Mean MMS was 29.5 ± 0.2, SEM, and BDI was 5.1 ± 0.8. Education quantified by the number of years spent in primary and secondary school was 11.7 ± 0.3 years. Ten of the 21 subjects qualified for (absence of claustrophobia and metal implants, six females, four males, age 60.4 ± 2.1 years, mean ± SEM) and agreed to undergo fMRI testing. The sample was recruited as a control group for a later comparison to stroke survivors. The study was approved by the Ethics Committee of the University of Tübingen, Germany. All participants provided written informed consent.

The weather prediction task (WPT) was performed as described by Knowlton et al. [1996]. The task is a forced-choice classification task with two alternative responses in which participants learn probabilistic associations between 14 different combinations of four playing cards (Fig. 1) and two weather outcomes, sun and rain. Each card was linked to an outcome with a prespecified probability (for sun: card 1–80%, card 2–54%, card 3–43%, card 4–20%). For each trial, either one, two, or three cards were shown composing 14 combinations that predicted the weather each with a certain combined probability. Table I shows

TABLE I. Predictive value, frequency and probabilities for card combinations

Combination	Combination class according to predictive value	Card				Percent of trials with combination	Probability for predicting sun
		1	2	3	4		
5	high	0	0	1	1	13%	0.08
1	medium	0	0	0	1	9.5%	0.11
7	medium	0	1	1	1	9.5%	0.11
3	low	0	1	0	1	6%	0.17
11	low	1	1	0	1	4.5%	0.22
6	low	0	1	1	0	4.5%	0.44
2	none	0	1	0	0	3%	0.5
13	none	1	0	1	1	3%	0.5
4	low	0	0	1	0	4.5%	0.55
9	low	1	0	0	1	4.5%	0.78
12	low	1	0	1	0	6%	0.83
8	medium	1	0	0	0	9.5%	0.89
14	medium	1	1	1	0	9.5%	0.89
10	high	1	1	0	0	13%	0.92

for each combination of cards the probability and how often the combination was shown (as a fraction of 150 trials). Presentation of combinations of cards, detection of button-press responses and feedback were computer-controlled using Matlab (Mathworks, Natick, MA) and Psychtoolbox (www.psychtoolbox.org). The WPT was verbally explained and demonstrated before the experiment. Participants were instructed not to talk with the investigator during the experiment. After presentation of a card combination, the subject had to respond within 4 s or the trial was scored as "incorrect." After 3 s, a prompt ("Please press a button") appeared on the screen. After pressing either the "sun" or the "rain" button, feedback was shown for 2 s in form of a smiley or a frowney face. Every 50 trials, a 1-min break was allowed. The experiment continued until 150 trials were completed.

Analysis of Behavioral Data

Trials were considered as "correct" when subjects chose the more probable weather (sun or rain) for the card combination presented. Trials in which subjects did not respond were scored as "incorrect." Missed responses were few and an alternative analysis that excluded those responses yielded results similar to the ones reported below.

To investigate the time course of learning, a learning curve (performance over time) was constructed for each subject using a two-step procedure. First, a cumulative performance curve was computed by adding 1 for each "correct" and subtracting 1 from each "incorrect" trial. This curve was then smoothed using spline interpolation (Matlab's spapi function, two knots). Second, to convert the cumulative into a performance-over-time curve the first derivative was computed (finder function). The resulting curve showed that performance increased in a nonlinear fashion over the course of training. Non-linear fitting of an exponential function [Boltzmann function, $p/(1 + \exp(k \times (a - x)))$] was used to derive parameters of learning: the plateau p, the turning point a of the sigmoid Boltzmann curve and the steepness in the turning point k. The plateau values were estimated for each card combination. A general linear model was used to explore whether the variability of the plateau was explained by sun versus rain, the combinations' predictive probability and its presentation frequency. Predictive probability was classified as high, medium or low (Table I). This stratification was done because some combinations were presented less frequently than others and by grouping we obtained prediction classed of approximately equal frequency. Whether or not a subject belonged to the subgroup receiving fMRI or not was included as an additional independent dichotomous variable to test for systematic differences between the samples.

In a second analysis, we measured how well single card combinations were remembered. We counted the number of trials in which the subject responded identical to a preceding trial with the same card combination and a smiley reward. The two trials could have been subsequent or several trials apart. Trials with the same response after a rewarded (smiley) trial will be referred to as "same-after-smiley" trials (SAS), otherwise they will be termed "opposite-after-smiley" (OAS). Conversely to examine, if subjects remembered to change their response behavior after seeing a frowney, we counted "opposite-after-frowney" (OAF) and "same-after-frowney" trials. The ratio of (SAS+OAF)/all trials was then used as an index of memory. Because memory improved during training, only the last 60 trials of 150 were considered to compute this index. Using the index as a dependent variable, we tested for effects of combination (sun versus rain), predictive value (high-medium-low, Table I) and feedback. The independent variable feedback was defined as the number of smileys - frowneys that a subject saw during the initial 30 trials of training. It was assumed that no relevant memory was formed during these initial 30 trials; hence, there was no bias towards smileys because some combinations had already been memorized. In fact frowneys were slightly but significantly more frequent during the initial 30 trials (1.9 vs. 2.8, $P = 0.045$) excluding a bias towards smileys. Whether or not a subject belonged to the subgroup receiving fMRI or not was included as an additional independent dichotomous variable to test for systematic differences between the samples.

JMP (version 8, SAS Institute, Cary, NC) was used for statistical calculations.

Functional Magnetic Resonance Imaging (fMRI)

Using a 3 Tesla scanner (Trio-Tim with eight-channel phased-array head coil, Siemens, Erlangen, Germany) fMRI was performed in subjects without metal implants or claustrophobia who agreed to participate. Visual cues were presented via a projection system installed in the scanner room; responses were collected using an MRI-compatible button-box. All participants responded using their right hand.

The WPT task was performed in participants naïve to this task as described above, except that the intertrial interval was 5 s, subjects had to respond within 4 seconds and did not receive the second prompt ("Please press a button"). Additionally, a control task was performed before and after the WPT to record brain activity related to visual processing and movement similar to the WPT. In the control task one, two or three cards were shown and subjects were asked to respond with the right button when two cards were presented and the left button when one or three cards were shown. Thirty training trials of the WPT were performed outside the scanner without feedback stimuli to avoid learning before the actual experiment was started. Brain activity during WPT was measured in three blocks of 50 trials each separated by 30 s of fixation. Fifty trials of the control task were performed before the WPT.

A high-resolution T1-weighted scan was acquired for anatomical localization. Functional imaging used gradient-echo planar T2*-weighted images (EPI) with

blood oxygenation level (BOLD)-contrast (TR = 2.4 s, TE = 30 ms, flip angle = 90°). Thirty-eight slices (slice thickness 3 mm) were acquired to cover the entire brain.

fMRI Analysis

fMRI data were processed using Brainvoyager QX (version 2.2, Brain Innovation BV, Maastricht, The Netherlands). BOLD-weighted EPI datasets were corrected for slice acquisition timing and head motion. Motion correction parameters were used as confound predictors in first-level GLM analyses. Datasets were registered to Talairach space in correspondence to the anatomical dataset. Images were spatially (Gaussian kernel, full-width at half-maximum of 8 mm) and temporally (three cycles, GLM-Fourier-high-pass-filter) smoothed.

The statistical analysis modeled each trial as two events, one before (presentation period) and one after the button press (feedback period). Five general linear models were computed:

1. In the first, the hemodynamic response was estimated for each of the following conditions, control trial presentation, control trial feedback, WPT trial presentation, WPT trial feedback. Random effects second-level analysis of variance (ANOVA) was used to construct WPT versus control activation maps for the presentation and feedback periods.
2. The second model was constructed analogous to Model 1 except for replacing the control trials with chance trials (combination with no predictive value).
3. In the third model, the WPT trials were separated according to whether the card combination predicted sun or rain, and according to the predictive value of the combination (prediction class, Table I). Random effects of ANOVA were used to extract activation maps for the effects of sun/rain, predictive value and their interaction (F tests). Contrasts (t tests) were computed for high > low predictive value and sun > rain. This second model was computed for presentation and feedback periods separately.
4. A fourth model was computed separating trials in which a smiley and a frowney feedback was received. Random effects ANOVA was then used to extract the activation map for smiley > frowney. Only the feedback period of the trial was included in this model.
5. In a fifth random effects ANOVA model we investigated a potential interaction between sun/rain and smiley/frowney as independent variables. This model did not yield any results and is therefore not further mentioned.

To test for effects of age, the subject sample was split according to the median age and the age group was included as a between-subject predictor in all models. For all random effects models the statistical threshold was set $P < 0.05$ corrected for multiple comparisons using a false discovery rate (FDR) method. Talairach coordinates and average p-values were measured for each activation cluster equal or larger than 10 voxels (10 × 3 mm × 3 mm × 3 mm).

RESULTS

Learning Depends on Repetition and Predictive Value of the Combination and on the Content of the Association Being Learned (Sun versus Rain)

During the task, performance (correct responses over time) increased in a sigmoid fashion reaching a plateau between trials 70 and 80 (Fig. 2A). For card combinations predicting sun plateau performance was higher than for card combinations predicting rain (general linear model, effect of the dichotomous variable sun/rain: $P = 0.039$, Fig. 2B) indicating that combinations predicting sun were better learned than those predicting rain. Plateau performance was also higher for combinations occurring more frequently (general linear model, effect of frequency: $P < 0.0001$, $r = 0.97$, Fig. 2C) and for those with higher predictive value, i.e., a larger difference from chance probability to predict either sun or rain (general linear model, effect of probability: $r = 0.84$, $P < 0.0001$, Fig. 2D). The latter effect, however, did not remain significant if frequency was included in the model. Whether or not the subject was in the fMRI group had no significant effect.

Learning Depends on Feedback

To evaluate learning from positive feedback, we counted how often a subject responded identical to a card combination that had occurred before and was rewarded with a smiley ("same-after-smiley," SAS). Vice versa, to evaluate learning from negative feedback we counted "opposite-after-frowney" (OAF) trials. SAS trials were significantly more frequent than OAF trials (paired t test, $P < 0.001$, Fig. 3a) indicating that card combinations leading to positive feedback were remembered better than those leading to negative feedback.

Using the SAS-CAF index (see Methods) as a measure of how well card combinations were remembered, learning was better for sun than rain combinations ($P = 0.036$) and for combinations for which more smileys than frowneys were received during the initial 30 trials of WPT training ($P = 0.001$, Fig. 3b). The interaction between the two independent variables was not significant. Likewise the predictive value of the combination (high-medium-low) had no significant effect if the variables sun/rain and smiley-frowneys were included in the model. Whether or not the subject was in the fMRI group had no significant effect.

Brain Activation

During the presentation period, the control task was associated with more activation in several brain areas as

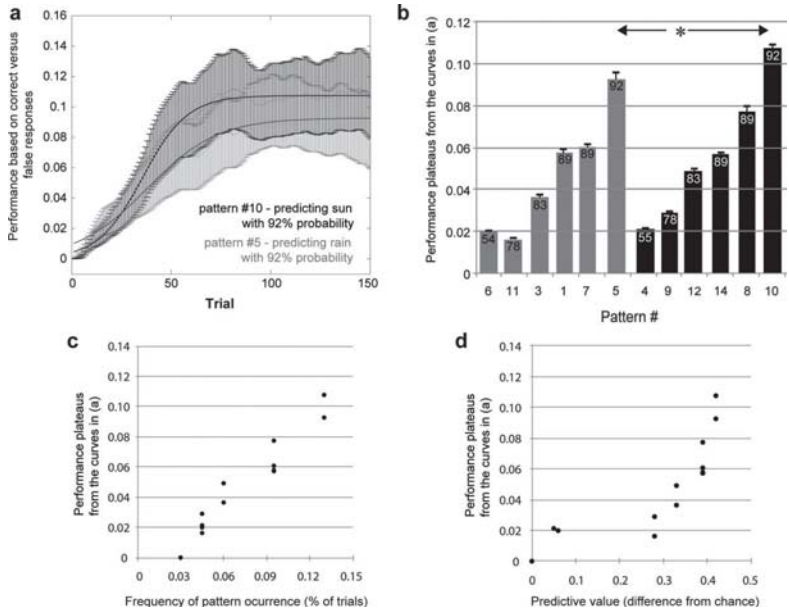

Figure 2.

Influence on learning. (**a**) Learning curves constructed from correct-versus-incorrect responses (see Methods) and averaged for all subjects are shown for the two card combinations with highest predictive value for sun (combination no. 10, red) and rain (combination no. 5, blue). Plateau performance is reached after approximately half the trials and is lower for rain than sun card combinations. Values on the *y*-axis represent the steepness, i.e., the first derivative of the cumulative performance curve, see Methods for details. (**b**) Plateau values estimated from the learning curves (examples in a) are shown for each card combination (bars indicate estimated plateau, error bars reflect SE, probabilities according to Table I). The plateaus are lower for card combinations predicting rain (blue) than for those predicting sun (red). This indicates that the emotional value of the learned content has an influence on learning efficacy. (**c**) Plateau values also depend on the frequency by which a card combination occurs and (**d**) on the predictive value of the card combination (difference from chance).

compared with the WPT (Table IIa). In contrast, during the feedback period, WPT lead to stronger activation in the left inferior frontal gyrus (Table IIb). In comparison with WPT card combinations without predictive value (chance trials), the combinations with a predictive value lead to stronger activation in the left posterior cingulum, Brodmann's area 31, during presentation (Table IIc). No differences between chance and predictive combinations were observed during feedback.

The third random effects ANOVA model tested the effect of combinations predicting sun- versus rain (content) and the combinations' predictive value (combinations grouped in high—92%, medium—89%, and low—83%, 78%, 55% to account for uneven frequency of presentation, Table I) on activation. For the presentation period of the trial, no significant voxels were found related to either the interaction or to the individual effects of content (sun/rain) or predictive value. For the feedback period, estimating the effect of the within-subject variable "predictive value" (high/medium/low) using an F test as well as the contrast (t test) high > low predictive value showed significant voxels in the right lateral cerebellum (Fig. 4, Table IIIa).

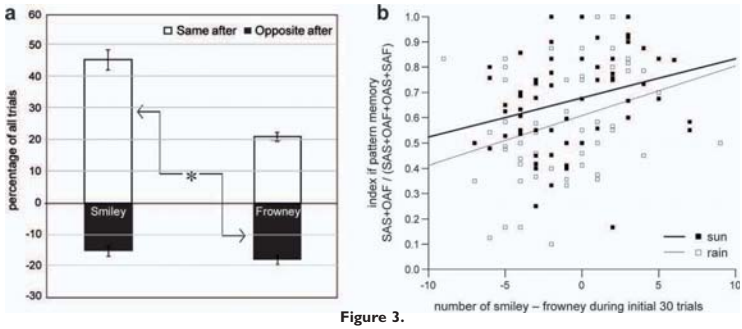

Figure 3.

(**a**) Smileys are better remembered than frowneys. If a smiley was presented, the subjects were more likely to give the same answer in the subsequent trial with the same card combination (yellow bars). In contrast, frowneys did not motivate the subjects to give the opposite answer (green bars, $*P < 0.001$). (**b**) The index of memory, computed as shown in the *y*-axis label, was related to how many smileys versus frowneys were received during the initial phase of WPT training and to whether sun or rain was predicted.

The forth random effects ANOVA model tested the effects of smiley versus frowney feedback during the feedback period of the trial. Smiley rewards were related to stronger activation in bilateral nucleus accumbens, bilateral posterior cingulum, left primary motor cortex, right postcentral gyrus, and right premotor cortex (Fig. 5, Table IIIb). No brain region was identified in which frowneys produced stronger activation than smileys.

Including age group (dichotomous variable by median split according to age) into the smiley-frowney model as a the between-subject variable revealed significant voxels in left cingulate gyrus, medial frontal gyrus and putamen (Table IV) for the interaction young>old × smiley>frowney. Including age group as a between-subject variable in the other statistical models did not reveal any significant results.

TABLE II. Brain activation (a) during presentation period of card combinations when observing Control Task > WPT Task (b) during feedback period when observing WPT Task > Control Task (c) during presentation period when observing WPT Trials > Chance Trials

Region of interest	Brodmann	Side	*x*	*y*	*z*	*t*	*P*
(a)							
Somatosensory cortex	3	left	−34	−23	42	−4.93	0.000109
Premotor cortex	6	left	−10	−2	60	−5.79	0.000017
Premotor cortex	6	left	−28	−2	45	−4.54	0.000254
Middle temporal gyrus	22	left	−55	−35	6	−9.37	0.000000
Orbitofrontal cortex	47	left	−49	31	−3	−6.94	0.000002
Thalamus		left	−1	−11	12	−5.97	0.000012
Putamen		left	−16	10	−6	−4.81	0.000141
Cerebellar hemisphere		left	−43	−47	−33	−4.91	0.000113
Premotor cortex	6	right	23	−5	45	−5.40	0.000040
Fusiform gyrus	20	right	50	−38	−24	−4.35	0.000385
Posterior cingulate	31	right	11	−32	33	−5.18	0.000064
Cerebellar hemisphere		right	14	−56	−33	−4.74	0.000165
(b)							
Inferior frontal gyrus	45	left	−49	28	9	6.48	0.000004
(c)							
Posterior cingulum	31	left	−19	−26	36	4.20	0.000539

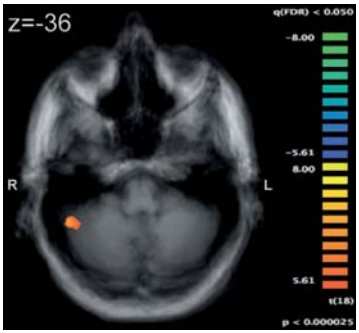

Figure 4.
Brain activation during the feedback phase of the trial reflecting the contrast "card combinations with high (according to Table I) > low predictive value." High value combinations recruited the lateral cerebellar hemisphere (threshold $P < 0.05$, FDR corrected).

DISCUSSION

These results demonstrate that learning efficacy in a probabilistic classification task depends on predictive value of the cue, the content (sun/rain) to be learned and the feedback (smiley/frowney) provided. Content and feedback seem to be independent factors. Memory of card combinations was better for combinations of cards with higher predictive value, for those combinations that predicted sun instead of rain, and if smiley feedback was provided. Higher predictive values lead to stronger activation of the lateral cerebellar hemisphere. Smiley feedback was associated with stronger activation of Nucleus accumbens (NAcc), sensorimotor cortex, and cingulum.

Subjects remembered card–weather associations markedly better when positive instead of negative feedback was provided. Wächter et al. [2009] reported a similar finding during implicit motor learning in healthy individuals. It may be that as individuals age negative feedback becomes more important as shown for avoidance learning in subjects with higher age (77 years) than our sample [Frank and Kong, 2008]. In fMRI smiley rewards were associated with stronger activation in bilateral NAcc (left>right; left dominance may be a consequence of right-hand button presses, [Haruno et al. 2004]). NAcc activation is frequently observed during reward processing [Aron et al., 2006; Bischoff-Grethe et al., 2009; Jensen et al., 2007; Linke et al., 2009; Poldrack et al., 2001; Seger and Cincotta, 2005; Ullsperger and von Cramon, 2003; Wachter et al., 2009]. During an over-learned cue-response task NAcc activation correlated with the amount of anticipated monetary reward [Knutson et al., 2001]. A metaanalysis of functional imaging studies on reward confirms bilateral activation of the NAcc and the posterior cingulum during positive versus negative feedback [Liu et al., 2010]. Also, the orbitofrontal cortex was reported to be overactive during presentation of reward versus punishment [Jensen et al., 2007; Liu et al., 2010] and reward prediction error [O'Doherty et al., 2003], but was not activated here. It is possible that this finding is related to the age of our subject sample; the frontal cortex is specifically vulnerable to age-related metabolic dysfunction [Curiati et al., 2011] and structural atrophy [Raz et al., 2004]. In support of this interpretation frontal cortex activation was stronger in the younger half of our subjects.

We found stronger activation of sensorimotor cortex (primary motor, premotor, and somatosensory cortex) with smiley than frowney feedback which has not been reported by reward studies using explicit learning paradigms. Paradigm differences may explain this discrepancy. Most reward studies use tasks that are overlearned, involve minimal learning or are not designed to learn

TABLE III. (a) Activation of cerebral regions observed in comparison of high predictive trials vs. low predictive trials in the feedback period. (b) Smiley-related activation in the feedback period as compared to frowneys

Region of interest	Brodmann	Side	*x*	*Y*	*z*	*t*	*P*
(a)							
Cerebellar hemisphere		right	47	−47	−36	6.97	0.000002
(b)							
Primary motor cortex	4	left	−28	−29	45	8.50	0.000014
Primary motor cortex	4	left	−37	−14	54	7.69	0.000030
Posterior cingulate	31	left	−16	−29	36	8.93	0.000009
Nucleus accumbens		left	−7	10	0	8.37	0.000015
Somatosensory cortex	3	right	44	−20	51	8.68	0.000012
Premotor cortex	6	right	11	−11	57	9.05	0.000008
Premotor cortex	6	right	8	−26	57	6.95	0.000067
Posterior cingulate	23	right	11	−35	27	9.70	0.000005
Posterior cingulate	31	right	23	−20	33	7.74	0.000029
Nucleus accumbens		right	10	7	−2	5.23	0.000585

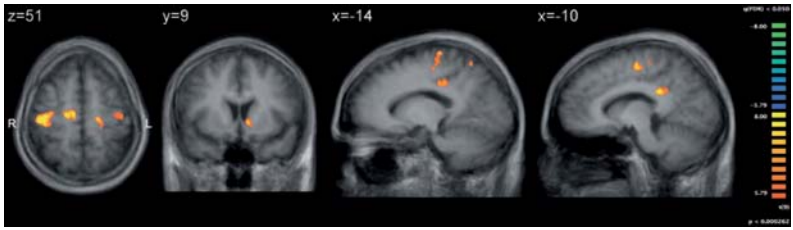

Figure 5.
Brain activation during the feedback phase of the trial reflecting the contrast "smiley > frowney feedback." Rewards (smileys) activated nucleus accumbens, sensorimotor and premotor cortices and cingulum more than negative (frowney) feedback (threshold $P < 0.05$, FDR corrected).

associations based on feedback [e.g., Elliott et al., 2003; Knutson et al., 2001]. Here, rewards were provided to learn associations between card combinations and outcomes. These associations were stochastic; hence, learning was largely implicit. Reward processing for implicit learning may involve the motor cortices like it does for motor skill learning [Wachter et al., 2009]. Whether this activation reflects a dopaminergic reward signal that is routed directly to motor cortex, remains speculative [Hosp et al., 2011; Molina-Luna et al., 2009].

The posterior cingulate cortex (PCC) was an additional brain region activated by positive > negative feedback confirming previous reports [Liu et al., 2010]. In primates, PCC activity corresponds to decisions deviating from a standard, i.e., decision salience [Heilbronner et al., 2011]. It has been proposed that the PCC detected change relative to a standard (expected) signal in general [Pearson et al., 2011]. In our context, positive rewards may have had greater impact on changing behavior than negative ones.

As expected, learning efficacy correlated directly with the card combination's predictive value. As compared to low predictive value, high-value trials over-activated the right lateral cerebellum. During sensorimotor learning, the cerebellum encodes error signals. Additional activation is unrelated to error [Imamizu and Kawato, 2009] and has been suggested to reflect the generation of an internal model that serves as a cognitive framework for task-related decisions [Ito, 2005]. One can speculate that cerebellar activation observed here for high > low predictive value trials reflects internal model formation for the classification task. High value trials are more informative than low-value trials for the formation of such a model. If cerebellar activity would represent an error signal, activation should have been stronger for low-value combinations, because for those subjects made more errors.

Combinations of cards predicting sun were better remembered than those predicting rain. Given everyday experience that positive events are better remembered than negative ones, this finding seems plausible in the context of explicit learning. That it transfers to implicit classification learning has—to our knowledge—not been reported before. That this finding is spurious and caused by receiving more smiley rewards for sun combinations was excluded by showing the smileys at the beginning of training were not more frequently presented for sun than rain trails. That this distribution became uneven later is expected because sun combinations were learned better and rewarded with more smileys. We also found statistically no interaction between the variables sun/rain and the number of smileys–frowney at the beginning of training in their effect on how well patterns were remembered. Nevertheless, was the behavioral difference between sun and rain trials small, which is probably why we did not observe a differential effect on brain activation.

The fMRI control task was chosen to subtract the activation related to visual presentation and motor response from performing the WPT. A comparison of the presentation phase of control and WPT trials showed stronger control-related activation in bilateral frontal, parietal and cerebellar areas. This likely reflects the fact that more intense processing was required for counting cards than for implicitly assessing their predictive value and deciding in favor of sun or rain during WPT. Counting is known to be

TABLE IV. Activation in the brain for the interaction young>old *x* smiley>frowney

Region of interest	Brodmann	Side	*x*	*y*	*z*	*t*	*P*
Posterior cingulate	23	left	−4	−32	27	26.6	0.000871
Anterior cingulate		left	−10	37	−3	30.2	0.000580
Medial frontal gyrus	32	left	−16	13	42	37.2	0.000289
Putamen		left	−13	7	−6	25.7	0.000967

associated with activation of fronto-temporal language areas, frontal and parietal cortices, and cerebellum [Ardila, 2010; Hinton et al., 2004; Kansaku et al., 2006; Sveljo et al., 2010]. During the feedback phase of a trial, findings were opposite in that the WPT was associated with stronger activation than control. This activation localized to the inferior frontal gyrus (Brodmann area 45). While this region is part of Broca's language area, it also is involved in risk assessment [d'Acremont et al., 2009]. Risk prediction error processing is likely more important during WPT than control.

A limitation of this study is that the individual valence of positive and negative stimuli was not assessed or controlled, neither for content nor feedback. Individuals may have found sun pleasant but rain rather neutral. This is a common criticism for many learning paradigms that focus on valence [Lang et al., 1990; Mneimne et al., 2010]. We used stimuli of small valence (smiley/frowney as feedback, imagined sun/rain as a response) to minimize potential differences in salience thereby hoping to reduce this confound. Although we think the effect is small, we cannot rule out a possible influence. A difference to prior fMRI studies using the WPT is that our control task was not interleaved with WPT trials. We chose this design to render the WPT data comparable to WPT training outside the scanner performed by subjects that did not qualify or opted against MR scanning. To minimize sequencing effects the control condition was performed before and after WPT training and for analysis the data of the two control periods were combined. A limitation to acknowledge is the small size of the fMRI sample. Nevertheless, random effects models that offer generalizability, yielded significant results. A limitation is also the advanced age of our subject sample. Subjects were collected as an age-matched control group for a comparison with individuals after a stroke to be reported elsewhere. Further studies are warranted to investigate the effects of feedback, content, and predictive value in young healthy subjects.

In conclusion, our data show that pleasant content and feedback improve implicit classification learning. Positive feedback is associated with stronger activation of NAcc, sensorimotor cortex, and posterior cingulum as compared with negative feedback. Learning also depends on the predictive value of the visual cues which is in part processed within the lateral cerebellum possibly reflecting the formation of an internal model.

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Impaired reward processing and reinforcement learning after stroke

Aims of this study, main findings, and own contributions

Principles of learning processes can be used to facilitate relearning skills and habits in stroke rehabilitation programs. In the previous study we showed that the provision of feedback in a procedural learning task seems to enhance performance during training. Moreover positive feedback and positive content seem to be more effective than negative ones.
In this fMRI study we used the weather prediction task to examine whether the processing of reward signals in the damaged brain is altered. Thirty stroke patients performed the task, and where possible underwent a fMRI scan during the performance.
Overall, learning in stroke patients was reduced as compared with controls. Smiley feedback did not have the same facilitation effect on learning in stroke as in controls. Brain activation in reward circuits (putamen, pallidum, thalamus, frontal cortex), cortical regions serving working memory (prefrontal cortex), and cerebellum was smaller in stroke patients than in controls. By masking out the lesioned areas we controlled that the lower brain activation in these areas did not result from damaged tissue. A lesion analysis showed a relationship between lesion location and performance in stroke patients. We divided the stroke patients into two groups using a learning index, and found that impaired learning performance was linked more with lesions in the frontal areas, the putamen, the thalamus, the caudate body and the insula. The important role of reward circuits for learning shown here might also serve as a further influential parameter along with clinical predictors regarding the effect of rehabilitation programs and might therefore explain partly the variability observed.

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Delineation of author contributions:

- I (JML) and ARL designed the study.
- I (JML) and ARL performed the data analysis.
- I (JML), TW and CG tested the participants.
- I (JML) wrote the manuscript.
- HOK and TW reviewed the manuscript.
- ARL wrote/reviewed the manuscript as supervising author.

Manuscript

Impaired reward processing and reinforcement learning after stroke

Judith M. Lam [a], Christoph Globas [b], Hans-Otto Karnath [a,c], Tobias Wächter [a,d]*, Andreas R. Luft [b]*

[a] Center of Neurology and Hertie Institute for Clinical Brain Research, University of Tübingen, Otfried-Müllerstr. 27, 72076 Tübingen, Germany

[b] Department of Neurology, University of Zürich, Frauenklinikstrasse 26, 8091 Zürich, Switzerland

[c] Department of Psychology, University of South Carolina, Columbia, SC 29016, USA

[e] German Center of Neurodegenerative Diseases (DZNE), Hoppe-Seyler-Str. 3, 72076 Tübingen, Germany

*both contributed equally.

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Correspondence:

Andreas R. Luft, MD, Department of Neurology, University of Zürich,

Frauenklinikstrasse 26, 8091 Zürich, Switzerland, Tel: +41 44 255 5400, Fax: +41 44 255 4649, andreas.luft@uzh.ch

Corresponding author: andreas.luft@uzh.ch

Abstract

Brain learning mechanisms are assumed to support successful rehabilitation and recovery after stroke. Hence, learning impairments may reduce the recovery potential. Here, the hypothesis is tested that stroke survivors have deficits in reinforcement learning that are related to abnormal processing of reward cues. Thirty stroke survivors and twenty-one healthy age-matched control subjects learned a probabilistic classification task with brain activation measured using functional magnetic resonance imaging in a subset of these individuals (stroke n = 17 and controls n = 10). Stroke subjects learned slower than controls to classify the cues. After being rewarded with a smiley face, they were less likely to give the same response when the cue was repeated. Stroke subjects showed reduced brain activation in reward circuits (putamen, pallidum, thalamus, frontal cortex), cortical regions serving working memory (prefrontal cortex) and cerebellum when compared with controls. Lesion analysis identified those stroke survivors as learning-impaired who had lesions in frontal areas, putamen, thalamus, caudate and insula. Lesion laterality had no effect on learning efficacy or brain activation. Taken together these findings suggest that stroke survivors have deficits in reinforcement learning that may be related to dysfunctional reward processing.

Corresponding author: andreas.luft@uzh.ch

Introduction

Learning may help to recover abilities that are impaired after brain injury. During learning and successful recovery, neurophysiological findings suggest plastic reorganization of cortical circuits as one underlying mechanism (Krakauer, 2006; Nudo, 2003; Schaechter, 2004). Consequently, many training principles for successful skill learning also support recovery (French et al., 2007).

Despite motor impairments after stroke, survivors retain the ability to learn new movement sequences (Ausenda and Carnovali, 2011; Boyd et al., 2010; Boyd and Winstein, 2004; Orrell et al., 2007; Vidoni and Boyd, 2009). Therefore, learning abilities may be utilized for rehabilitation. But some patients suffer from learning deficits. Impaired proprioception and basal ganglia function have been proposed as the cause of this finding (Boyd et al., 2009; Vidoni and Boyd, 2009).

Previous studies of learning after stroke have focused on motor skill learning because of its implications in movement recovery. Motor skill learning is a special form of implicit learning. Like many other forms of learning it relies in part on reinforcement in the form of reward signals that are encoded in the frontal cortex-basal ganglia network (Lam et al., 2012; Wachter et al., 2009) . Training that combines movement with feedback provides therapeutic benefits after stroke (Jonsdottir et al., 2010; van Vliet and Wulf, 2006).

Here, stroke survivors were trained in a feedback-driven implicit classification task (Keri et al., 2000; Knowlton et al., 1996; Perretta et al., 2005; Poldrack et al., 2001). This task is known to involve reward processing regions like the striatum in healthy young adults (2001). Patients with Parkinson's disease have difficulties learning this task (Shohamy et al., 2004).

Corresponding author: andreas.luft@uzh.ch

We hypothesized that stroke survivors with lesions to basal ganglia and other reward regions have impaired reward processing leading to a deficit in reinforcement learning.

Corresponding author: andreas.luft@uzh.ch

Materials and Methods

Subjects and Task

Twenty-one healthy elderly subjects (control) and 30 stroke survivors were recruited via advertisements. An analysis of the data of control subjects was published previously (Lam et al., 2012). Stroke patients were included if they had suffered an ischemic stroke, confirmed by MRI, six or more months before enrollment. Exclusion criteria for all participants were visual impairments, a Mini Mental Status exam (MMS) < 27 points and Beck's Depression Index (BDI) > 11 points. In all patients, structural MRI scans of the ischemic lesion were performed. Ten of the 21 control subjects and 17 of the 30 stroke survivors underwent fMRI testing. The study was approved by the Ethics Committee of the University of Tübingen, Germany. All participants provided written informed consent.

The weather prediction task (WPT) was performed as described by Knowlton and coworkers (1996). The task is a two-alternative forced-choice classification task in which participants learn probabilistic associations between 14 different combinations of four playing cards and two weather outcomes, sun and rain. Each card is associated with an outcome with a pre-specified probability (for sun: card 1 - 80%, card 2 - 54%, card 3 - 43%, card 4 - 20%, vice versa for the outcome rain). Either one, two or three cards are presented composing 14 different combinations that predict the weather with a certain probability. **Table I** shows for each combination of cards the probability and how often the combinations were presented during the 150 trial training period. Predictive probability was classified as high, medium or low. This stratification was done because some combinations were presented less frequently

Corresponding author: andreas.luft@uzh.ch

than others. By grouping we obtained prediction classes of approximately equal frequency.

Each trial consisted of the presentation of a card combination and the response of the subject – („sun“ or „rain”) by pressing one of two buttons followed by feedback in form of a smiley or a frowney face. For example, for card combination 10 (**Table I**) 92% of the trials required a „sun“ response and 8% a rain response to see only smileys. Otherwise, frowneys were shown. The paradigm was implemented using Matlab (Mathworks Inc, Natick, MA, USA) and Psychtoolbox (www.psychtoolbox.org).

The WPT was verbally explained and briefly trained before the experiment (on average 20 trials). This practice ensured that participants became used to the procedure. Neutral faces were shown as feedback during practice trials. Participants were instructed not to talk with the investigator during the entire experiment. After presentation of a card combination, the subject had to respond within 4 seconds or the trial was scored as “incorrect”. After 3 seconds, a prompt („Please press a button“) appeared on the screen. After pressing either the „sun“ or the „rain“ button, feedback was shown for 2 seconds. After every 50 trials a one-minute break was allowed. One experiment included 150 trials.

[Table I approximately here]

Analysis of behavioral data

Trials were scored as “correct” when subjects chose the optimal response, that is the more probable weather (sun or rain) for the card combination presented, e.g., for card combination 10 (**Table I**) all trials in which they responded with „sun“ were counted as “correct”. This was not identical to the response that would have always

Corresponding author: andreas.luft@uzh.ch

led to a smiley reward (see above). Trials in which subjects did not respond were scored as “incorrect”. The percentage of missed responses was calculated and compared between groups.

Behavioral data were analyzed either by plotting the percentage of correct responses for every 30 trials to obtain a learning curve or by measuring how well single card combinations were remembered. For the latter analysis, trials in which the subject responded identical to a preceding trial where the same card combination had been rewarded with a smiley (same response after smiley, SAS), were counted. The two trials could have been subsequent or several trials apart. An index of memory was calculated by the ratio of the number of SAS and all smiley trials (= SAS / (SAS + OAS); OAS: opposite response after smiley). Conversely, to examine if subjects remembered to change their response behavior after seeing a frowney, we counted „opposite response after frowney“ (OAF) and „same response after frowney“ trials.

Additionally, reaction times between presentation of the card combination and the subject’s response were recorded and compared between groups.

For statistical testing JMP (version 8, SAS Institute Inc, Cary, NC, USA) was used. Learning curves were compared between groups using repeated measures ANOVA. Sphericity was assessed using Mauchly‘s test and Greenhouse-Geisser (G-G) correction was applied if the test was significant. SAS/(SAS+OAS) ratios were compared using ANOVA with group as between-subject factor and pattern as within-subject factor including the interaction of the two.

Functional magnetic resonance imaging (fMRI)

A 3 Tesla scanner (Trio-Tim with 8-channel phased-array head coil, Siemens, Erlangen, Germany) was used. Visual cues were presented via a projection system

Corresponding author: andreas.luft@uzh.ch

installed in the scanner room. Responses were collected using an MRI-compatible button-box.

The WPT was performed in participants naïve to this task as described above except that the intertrial interval was 5 seconds, subjects had to respond within 4 seconds and did not receive written prompts („Please press a button“). A control task was included before the WPT to record brain activity related to visual processing and movement comparable to the WPT. In the control task, one, two or three cards were shown. Subjects were asked to respond with the right button when two cards were presented and the left button when one or three cards were shown. Thirty practice trials were performed outside the scanner in which neutral faces were shown as feedback to avoid learning before the definitive experiment began. Brain activity during WPT was measured during three blocks of 50 trials each separated by 30 seconds of fixation. Fifty trials of the control task were performed before the WPT.

A high-resolution T1-weighted scan was acquired for anatomical localization. Functional imaging was performed using a gradient-echo planar T2*-weighted sequence with blood oxygenation level (BOLD)-contrast (TR=2.4 s, TE=30 ms, flip angle=90°). Thirty-eight slices (slice thickness 3 mm) were acquired to cover the entire brain.

fMRI Analysis

We used Brainvoyager QX (version 2.2, Brain Innovation BV, Maastricht, The Netherlands) to transform the anatomical data into Talairach space and process the fMRI data. Talairach transformation involves two steps. First, the brain is rotated so that the anterior-posterior commissure plane is horizontal. Then the brain is warped into the standard space after defining its boundaries (anterior, posterior, superior,

Corresponding author: andreas.luft@uzh.ch

inferior, right, and left). Visual inspection of the Talairach transformation was done by two investigators to ensure a plausible result without tissue shrinked or stretched into lesioned areas. BOLD-weighted EPI datasets were corrected for slice acquisition timing and head motion. Motion correction parameters were used as confound predictors in first-level GLM analyses. Datasets were registered to Talairach space in correspondence to the anatomical dataset. Images were spatially (Gaussian kernel, full-width at half-maximum of 8 mm) and temporally (3 cycles, GLM-Fourier-high-pass-filter) smoothed.

The statistical analysis modeled each trial as two events, one before (*presentation*) and one after the button press (*feedback*). Two random effects general linear models were computed, one for each type of event:

1. *Presentation*: This model included *group* (stroke/control), *predictive value* (high/medium/low probability, **Table I**), and *sun/rain* as independent variables.
2. *Feedback*: This model included *group* (stroke/control) and *smiley/frowney* as independent variables.

T-tests were used to construct statistical maps for contrasts of independent variables. The statistical threshold was Bonferroni-corrected for multiple comparisons. Talairach coordinates of the center, the number of voxels above the statistical threshold and average p-values were measured for each cluster of activation that was equal or larger than 10 voxels (10 x 3mm x 3mm x 3mm).

Lesion analysis

MRI datasets with right-sided lesions were flipped so that the lesion was on the left side for all subjects. For each individual, the boundary of the lesion was then manually delineated by one experimenter (JML) on every consecutive axial slice

Corresponding author: andreas.luft@uzh.ch

showing the lesion. MRIcron software was used ((Rorden et al., 2007), http://www.mccauslandcenter.sc.edu/mricro/ mricron/). The extension and location of the lesion shapes were controlled by a stroke neurologist (CG).

We employed two types of statistical voxel-wise lesion-behavior mapping (VLBM) analyses. First, using the t-test statistic implemented in the MRIcron toolset we computed a voxel-based lesion symptom mapping (Rorden et al., 2007) relating lesions to a measure of learning performance, i.e., the slope of the learning curve (linear regression coefficient) and the memory index SAS/(SAS+OAS). We controlled for multiple comparisons by using the False Discovery Rate (FDR) correction. Second, we performed a subtraction analysis (Rorden and Karnath, 2004) between two subgroups of stroke patients, namely good learners versus poor learners. Poor learners were those with a slope or memory index one standard deviation or more below the mean of the control sample. The resulting subtraction plots display the frequency (in percent) by which an area is more frequently lesioned in poor compared to good learners (e.g. a value of 10% indicates that a voxel is lesioned 10% more frequently in poor learners than in good learners). To evaluate the resulting statistical maps with respect to cortical and subcortical gray matter structures, we used the Talairach daemon ((Lancaster et al., 2000), http://www.talairach.org/).

Corresponding author: andreas.luft@uzh.ch

Results

Sample characteristics

Stroke and control subjects did not differ in age, Mini Mental Status, Becks Depression Inventory, Motivation and Life satisfaction Index. There were more male subjects in the stroke group but more females among controls. Control subjects reported significantly more years of education than stroke participants (**Table IIA**). fMRI subsets of neither stroke nor control groups differed from the respective full datasets in demographic, stroke-related or outcome-related variables (**Table IIB**).

[Table II approximately here]

Classification learning

Classification learning was impaired in stroke subjects. For the card combination associated with sun in 92% of trials, controls improved their performance, i.e. the number of correct responses, faster than in stroke survivors and reached a higher plateau (repeated-measures ANOVA, interaction effect of *trial* × *group*, G-G corrected: p=0.0355, **Figure 1A** shows learning curves). Linear regression coefficients computed for each subject's learning curve were lower in stroke than control (t-test, p=0.0165, **Figure 1B**). No differences between control and stroke subjects were observed for other card combinations, which were generally learned to a lesser degree as previously reported (Lam et al., 2012).

[Figure 1 approximately here]

Stroke subjects remembered a card combination poorly. The percentage of „same response after smiley" trials [SAS / (SAS + OAF)], an index of memory, was significantly lower in stroke than control participants (ANOVA, interaction effect of

Corresponding author: andreas.luft@uzh.ch

pattern × *group*: p=0.0483). The difference was most pronounced for the „92% sun"-card combination (**Figure 2**). No differences between groups were found for OAF/(OAF+SAF).

In both statistical models age, gender, side and location of lesion were initially included as independent variables but were removed after they showed no significant effects.

Reaction times between presentation and response did not differ between stroke and control subjects in the entire sample (mean±SD, control: 1.65±0.49, stroke: 1.66±0.37, p=0.96) as well as for the subsets of participants undergoing fMRI (control: 1.42±0.39, stroke: 1.53±0.36, p=0.44).

The percentage of missed response, i.e., when subjects did not press a button in the required time frame, was low and did not differ between groups (entire sample: mean±SD, control: 0.76%±1.52%, stroke:0.62%±1.05%, p=0.70; fMRI subset: control: 0.47%±1.52%, stroke:0.82%±1.05%, p=0.42).

[Figure 2 approximately here]

Brain activation during classification learning

During presentation, i.e., the period from seeing the card combination to pressing the response button, stroke subjects showed less brain activation than controls. The model analyzing presentation included *predictive value* (pattern class), *sun/rain* and *group* as independent variables. Neither of the two-way interactions (*predictive value* × *group*, *sun/rain* × *group*) yielded significant voxels. The F-test for *group*, however, revealed a large number of significant voxels. We therefore computed a t-test for the contrast *control* > *stroke* that resulted in highly significant voxels (Bonferroni-corrected $p < 0.00005$) in the right inferior frontal gyrus, basal ganglia, thalamus and

Corresponding author: andreas.luft@uzh.ch

cerebellum, and in the left insula, inferior frontal and precentral gyri, thalamus, cerebellum and pons (**Table III, Figure 3A**). Estimated beta values for these regions were not correlated with the individual learning performance as measured using the total number of correct responses or the SAS/(SAS+OAS) ratio. No region was found to be more active in stroke than in control subjects.

[Table III approximately here]

Within the stroke cohort, activation during presentation was found in right cerebellum, frontal (BA 9, 10), parietal lobe (BA 7) and cingulate gyrus (BA 32, random effects $p<0.05$ FDR corrected).

During feedback, i.e., the period from pressing the response button to seeing the next card combination, smiley feedback produced less brain activation in stroke than in control subjects. The model analyzing feedback events included *group* and *smiley/frowney* as independent variables. The interaction *group* × *smiley/frowney* (F-test) revealed large areas of activation in both cerebral hemispheres and in the cerebellum. Hence, two t-tests contrasting the groups (*control* > *stroke*) for either smiley or frowney trials were computed. Smiley feedback was associated with stronger activation in the right putamen and bilaterally in the cerebellar anterior lobe (**Figure 3B, Table IV**). No between-group differences were found for frowney feedback. We then tested for correlations between estimated beta values for each region and the index of how well smileys were remembered, i.e., SAS/(SAS-OAS). No significant correlations were observed.

[Table IV, Figure 3 approximately here]

Corresponding author: andreas.luft@uzh.ch

Comparing these regions underactive in stroke with the individual lesion showed no overlap except in one stroke survivor (**Figure 4**).

[Figure 4 approximately here]

Within the stroke cohort, activation during feedback was found in bilateral cerebellum, bilateral parietal (BA 7, 40), left frontal (BA 8, 9, 47) and temporal lobes (BA 21, random effects $p<0.05$ FDR corrected).

Lesion side and location

An overlay of all lesions showed that the brain region most commonly injured (n=13) was the premotor cortex (center Talairach coordinates: x=-22, y=-8, z=34, **Figure 5**).

[Figure 4 approximately here]

Indices of learning or memory did not differ between patients with left-sided (n=11) and right-sided lesions (n=6). Random effect models found no difference in brain activation between these groups. The VLSM analysis performed on the continuous measures indexing learning performance (the slope of learning curve and the memory index SAS/(SAS+OAS)) did not reveal any significant voxel after controlling for multiple comparisons. In a subtraction analysis we then contrasted good with poor learners (patients with a value better respectively worse than one standard deviation below the mean of the control sample, i.e., for slope: mean = 0.073, STDEV = 0.066, for memory index: mean = 0.800, STDEV = 0.206). For the slope of the learning curve (i.e. learning efficacy) the subtraction plot in **Figure 6A** revealed that poor learners were more likely to have lesions in the putamen (11%), thalamus (11%), caudate nucleus (body, 6%), insula (6%) and the orbitofrontal cortex (Brodmann area 10, up to 22%). For the memory index the subtraction plot (**Figure**

Corresponding author: andreas.luft@uzh.ch

6B) revealed that patients with poor memory often (between 30-40%) had lesions in frontal cortex (BA 10), putamen, caudate, temporal cortex and the insula.

[Figure 6 approximately here]

Corresponding author: andreas.luft@uzh.ch

Discussion

These findings demonstrate that stroke survivors have deficits in reinforcement-based classification learning, both for associating card combinations with weather outcomes as well as for remembering single trials that had previously been rewarded with smileys. A possible explanation for these deficits is impaired reward processing due to lesions in networks of the brain that deal with reinforcement signals.

The weather prediction task involves learning probabilistic associations between a visual cue and a dichotomous response. We have previously shown that healthy individuals learn best if the predictive value of a cue is high and if they are rewarded instead of being punished, even if feedback is given in the form of weak stimuli such as smiley and frowney faces (Lam et al., 2012; Wachter et al., 2009). Stroke patients regardless of their age, gender or lesion location showed reduced learning and memorization. The difference was expectedly higher for card combination with high predictive value that stimulated the highest degree of learning (compare **Figure 1**).

In search for a reason for this deficit we analyzed brain activation during learning. Using our previously published approach (Lam et al., 2012) we separated presentation and feedback phases of a trial. During presentation, control subjects showed stronger brain activation than stroke subjects regardless of the predictive value of the card combination. During feedback, control subjects demonstrated higher activation than stroke survivors in putamen and cerebellum. Comparing lesions with fMRI patterns excluded the fact that the under-activation was simply the consequence of tissue loss in these areas.

The activated brain regions are part of reward and working memory circuits. Putamen, pallidum, thalamus, frontal cortex, insula and brainstem are activated in

Corresponding author: andreas.luft@uzh.ch

reward paradigms (Liu et al., 2011). Insula and frontal regions are preferentially recruited during reward anticipation (Knutson et al., 2001). Alternatively, frontal regions (Brodmann‘s areas 44-46) may reflect the involvement of working memory processes (Seamans and Yang, 2004). Implicit learning is impaired after prefrontal lesions (Barker et al., 2004; Chase et al., 2008) and probabilistic classification learning is facilitated by direct current stimulation of the prefrontal cortex (Kincses et al., 2004). Patients with basal ganglia lesions have deficits in reward-based reversal learning (Bellebaum et al., 2008). This supports our observation of reduced activation in the putamen of our stroke subjects and their diminished performance.

The cerebellum is not among regions typically involved in reward or memory processes. But, the cerebellar role in procedural (motor sequence) learning and classical eye blink conditioning is well established (Hikosaka et al., 1999). In motor learning it is involved in the training-induced adaptation of movements by integrating sensory feedback (Seidler et al., 2002). This is well in accordance with our finding of cerebellar activation during the feedback (reward/punishment) phase. The anatomical architecture of the mossy fiber and climbing fiber network may be specifically apt to integrate reinforcement signals (Swain et al., 2011). Thoma and coworkers (2008) showed deficits in reinforcement learning in cerebellar patients. Ramnani et al. (2004) reported cerebellar activation related to rewards. A resting state analysis suggested the cerebellum to be functionally connected with the nucleus accumbens (Cauda et al., 2011), an area known to receive reward-related signals. The cerebellum interacting with the forebrain may be involved in motivation and in integrating information about the reinforcer, its predictive value and strength (Swain et al., 2011). Decreased cerebellar recruitment in stroke patients may reflect

Corresponding author: andreas.luft@uzh.ch

reduced motivation and their inability to value reinforcing cues. Decreased activation in classical reward networks may indicate a deficit in reward signal processing itself.

In our analysis, lesion side did not affect learning behavior, although this observation is compromised by small and disproportionate samples sizes. While the VLSM analysis did not reveal areas associated with impaired learning after controlling for multiple comparisons (probably due to sample size), the voxel wise subtraction analysis showed that poor learners frequently (up to 22%) had lesions in areas related to reward processing (putamen, thalamus, insula, orbitofrontal cortex) as well as the caudate nucleus. Patients with lower memory indices had more frequently (up to 40%) lesions in frontal, temporal, insular and striatal areas. The involvement of the caudate nucleus in classification learning has been reported before (Seger and Cincotta, 2005). These authors showed that the activation of the caudate body was strongly associated with successful learning. Activation of the caudate head is related to feedback processing (Delgado et al., 2004). Although these results are in accordance with the fMRI results discussed above, they have to be interpreted carefully due to the small sample size and the imbalance between good learners (n(slope/memory Index)=19/20) and poor learners (n=11/10).

Corresponding author: andreas.luft@uzh.ch

Conclusion

Our study demonstrates abnormal processing of reward cues in stroke survivors resulting either from lesioned or dysfunctional brain reward circuits. These deficits may be responsible for learning impairments after stroke. Learning deficits may hinder recovery and rehabilitation. Further studies are needed to test, whether rewards with higher valence can overcome these deficits in reinforcement learning by more strongly recruiting reward circuits. Such a finding would have an impact on post-stroke rehabilitation programs.

Corresponding author: andreas.luft@uzh.ch

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Corresponding author: andreas.luft@uzh.ch

Figure Legends

Figure 1. **Stroke subjects learn an association between a card combination and sun (92% predictive probability) slower than age-matched healthy subjects.** (**A**) The percentage of trials for which subjects responded with „sun“ – the optimal response (=“correct response“) – increases in control more than in stroke patients during training over 150 trials. (**B**) Mean linear regression coefficients for individual learning curves like the curve shown in a), are significantly higher for control than for stroke subjects (* $p<0.05$, error bars indicate SEM).

Figure 2. Stroke subjects remember card combinations less than controls. The percentage of trials in which subjects gave the same response to a card combination like in a previous trial in which the same combination was rewarded („same response after smiley“ – SAS), relative to all smiley trials (SAS + „opposite response after smiley“, OAS) was higher in control than in stroke subjects. The difference was most pronounced for card combinations with high predictive value (92% sun and rain).

Figure 3. **(A)** For **presentation** (seeing the card combination until pressing the response button), the differences in brain activation between groups (control > stroke subjects) are found in areas involved in reward processing, working memory and motivation (compare **Table III**). **(B)** For **smiley feedback** (pressing the response button until seeing the next card combination, trials in which smileys were shown), the differences in brain activation between groups (control > stroke subjects) are found in areas involved in reward processing and motivation (compare **Table IV**).

Corresponding author: andreas.luft@uzh.ch

Figure 4. Lesion overlay of fMRI subsample of stroke patients. The degree of overlap (number of lesions overlapping) is color-coded from violet (n=1) to red (n=max. number of subjects). The same slice positions are presented as in Figure 3. Talairach y-coordinates of the coronal sections are provided.

Figure 5. Subtraction plot of poor learners minus good learners. Lesion differences between good and poor learners are illustrated by a color-coding the frequency (in percent) by which an area is more frequently lesioned in poor compared to good learners. Poor learners were defined as those patients whose **(A)** learning slope or **(B)** memory index were one standard deviation below the mean of control sample. Talairach z-coordinates of the axial sections are given.

Figure 6. Lesion overlay of stroke survivors. The axial slices correspond to the slices shown in Figure 5. The degree of overlap (number of lesions overlapping) is color-coded from violet (n=1) to red (n=30). Most overlap (n=13) was observed for premotor cortex.

Corresponding author: andreas.luft@uzh.ch

Figures

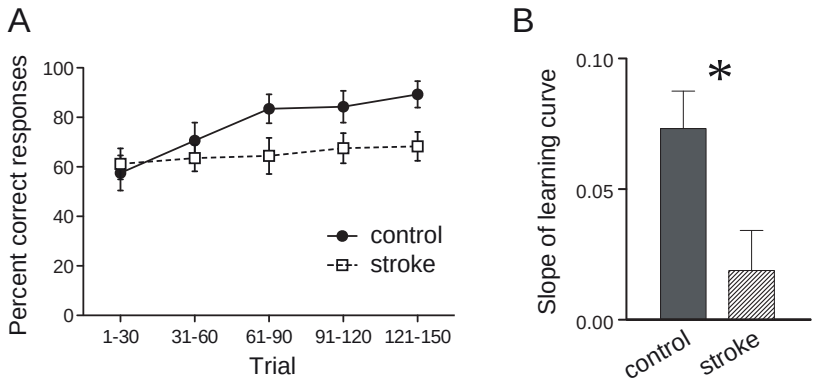
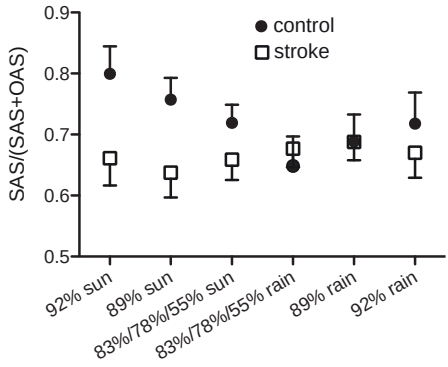


Figure 1.



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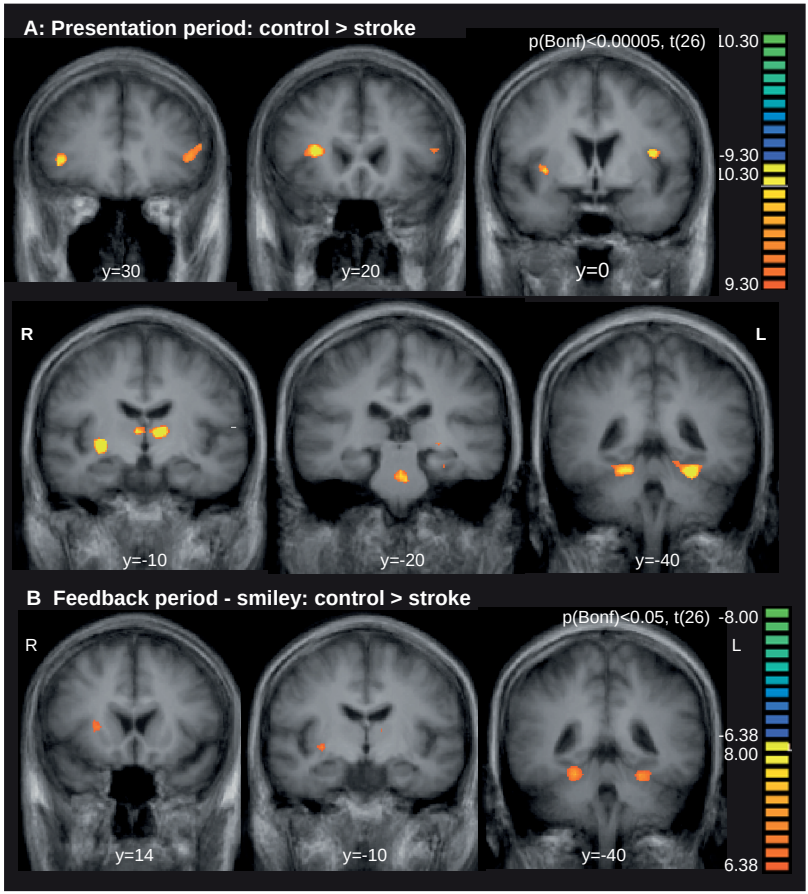

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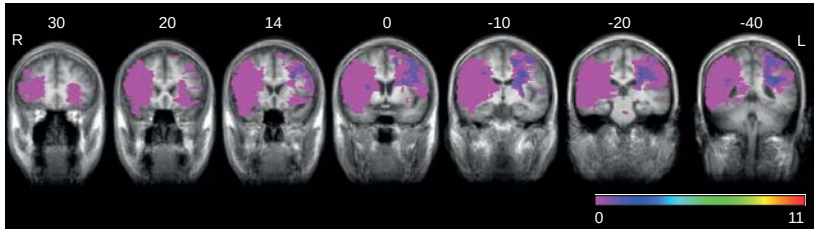

Figure 4.

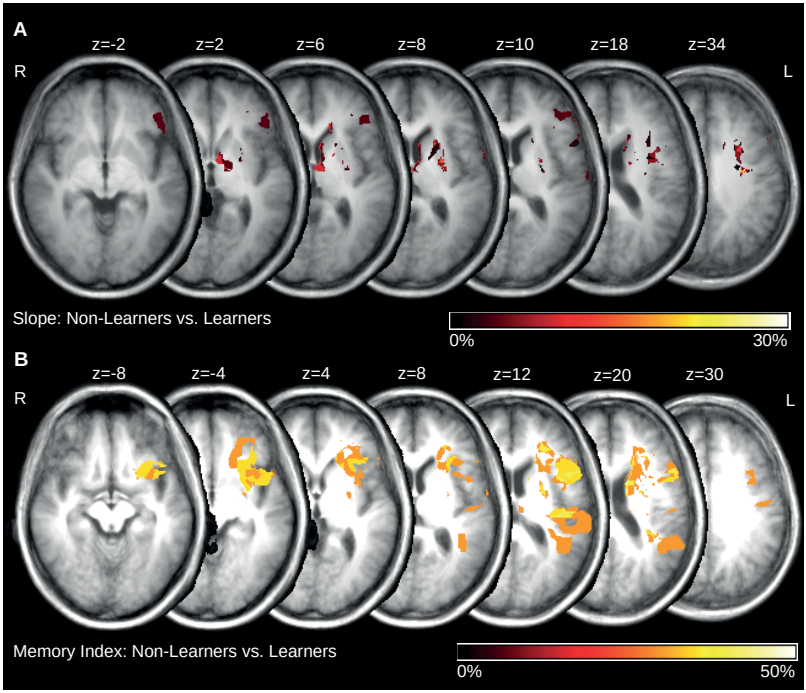

Figure 5.

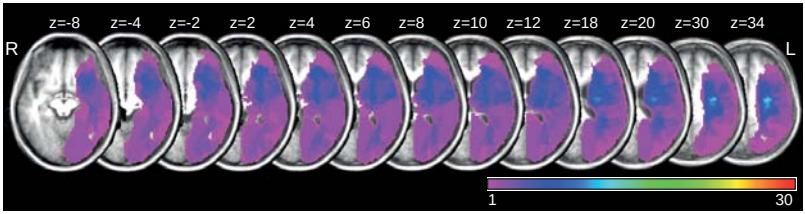

Figure 6.

Tables

Table I: Card combinations with their predictive value and presentation frequency.

		Card					
Combi-nation	Combination class according to predictive value	1	2	3	4	Percent of trials with combination	Probability for predicting sun
5	high	0	0	1	1	13 %	0.08
1	medium	0	0	0	1	9.5 %	0.11
7	medium	0	1	1	1	9.5 %	0.11
3	low	0	1	0	1	6 %	0.17
11	low	1	1	0	1	4.5 %	0.22
6	low	0	1	1	0	4.5 %	0.44
2	none	0	1	0	0	3 %	0.5
13	none	1	0	1	1	3 %	0.5
4	low	0	0	1	0	4.5 %	0.55
9	low	1	0	0	1	4.5 %	0.78
12	low	1	0	1	0	6 %	0.83
8	medium	1	0	0	0	9.5 %	0.89
14	medium	1	1	1	0	9.5 %	0.89
10	high	1	1	0	0	13 %	0.92

Table II. Demographic and stroke-related parameters.

A. Control sample compared to stroke sample			
	Controls	Stroke	p
n	21	30	
Age (mean, SD)	64.6 (9.7)	60.83 (6.95)	0.91 [b]
Gender (f/m)	14/7	7/23	0.002 [c]
MMS (mean, SD)	29.5 (0.91)	29.10 (1.18)	0.27 [b]
BDI (mean, SD)	5.13 (3.12)	5.07 (3.16)	0.96 [b]
Education (ys, mean, SD)	11.65 (1.39)	9.79 (1.80)	<0.001 [b]
SOS-Total (mean, SD)[a]	44.73 (5.92)	45.68 (3.88)	0.53 [b]
SOS-Importance (mean, SD)[a]	20.87 (4.36)	21.96 (2.72)	0.39 [b]
SOS – Effort (mean, SD)[a]	23.87 (2.1)	23.71 (2.19)	0.83 [b]
Life Quality (mean, SD)	31 (6.98)	29.87 5.78)	0.57
B. All stroke patients compare to fMRI subsample			
	All	fMRI data set	p
n	30	17	
Age (mean, SD)	60.83 (6.95)	61.82 (6.35)	0.15 [b]
Gender (f/m)	7/23	6/11	0.38 [c]
Lesioned hemisphere (l/r)	19/11	11/6	0.93 [c]
Lesion location(c/sc)	15/15	7/10	0.56 [c]
Time since stroke in months (Mean, SD)	54,95 (47,61)	38,21(20,54)	0.26*
MMS (mean, SD)	29.10 (1.18)	29.12 (1.17)	0.95 [b]
BDI (mean, SD)	5.07 (3.16)	4.06 (2.99)	0.29 [b]
NIHSS (mean, SD)	2.8 (2.68)	1.82 (2.19)	0.21 [b]
BI (mean, SD)	95.50 (8.13)	99.41 (2.43)	0.02 [b]
Education (ys, mean, SD)	9.79 (1.80)	9.53 (1.77)	0.63 [b]
SOS-Total (mean, SD)	45.68 (3.88)	46.65 (3.37)	0.4 [b]
SOS-Importance (mean, SD)	21.96 (2.72)	22.59 (2.76)	0.45 [b]
SOS – Effort (mean, SD)	23.71 (2.19)	24.06 (1.60)	0.58 [b]
Life Quality (mean, SD)	29.87 (5.78)	31 (5.26)	0.51 [b]

[a]SOS = Student Opinion Scale, [b] t-test; [c] Chi-Square-Pearson coefficient

Table III. Regions activated during the presentation phase in control > stroke subjects (random effects model)

Number	Region	side	number of voxels	x	y	z	t
1	Inferior Frontal Gyrus, Brodmann area 45	right	430	38	28	6	11.3
2	Putamen	right	1'984	29	-8	0	12.8
3	Medial Globus Pallidus	right	132	17	-8	-6	10.3
4	Thalamus, Medial Dorsal Nucleus	right	98	5	-11	9	10.6
5	Cerebellum, Anterior Lobe	right	2'756	17	-44	-15	11.2
6	Insula, Brodmann area 13	left	375	-34	-2	15	11.0
7	Precentral Gyrus, Brodmann area 44	left	68	-55	10	9	9.72
8	Inferior Frontal Gyrus, Brodmann area 46	left	603	-49	28	15	10.9
9	Thalamus, Ventral Lateral Nucleus	left	471	-10	-11	9	11.4
10	Cerebellum, Anterior Lobe	left	2363	-22	-41	-15	11.2
11	Pons	left	169	-4	-23	-24	10.1

Table IV. Regions activated by smiley feedback in controls > stroke subjects (random effects model)

Number	Region	side	number of voxels	x	y	z	t
1	Putamen	right	322	29	-14	0	6.78
2	Cerebellum, Anterior Lobe	right	2278	22	-41	-15	7.64
3	Putamen	right	282	23	13	9	7.00
4	Cerebellum, Anterior Lobe	left	898	-25	-44	-15	7.36

List of Publications

- Lam, J. M.; Globas, C.; Cerny, J.; Hertler, B.; Uludag, K.; Forrester, L. W.; Macko, R. F.; Hanley, D. F.; Becker, C. & Luft, A. R. Predictors of response to treadmill exercise in stroke survivors. Neurorehabil Neural Repair, 2010, 24, 567-574.
- Globas, C.; Lam, J.M.; Zhang, W.; Imanbayev, A.; Hertler, B.; Becker, C.; Whitall, J.; McCombe-Waller, S.; Mori, S.; Hanley, D.F. & Luft, A.R.. Mesencephalic corticospinal atrophy predicts baseline deficit but not response to unilateral or bilateral arm training in chronic stroke. Neurorehabil Neural Repair, 2011, 25, 81-87.
- Globas, C.; Becker, C.; Cerny, J.; Lam, J.M.; Lindemann, U.; Forrester, L.W.; Macko, R.F. & Luft, A.R. Chronic stroke survivors benefit from high-intensity aerobic treadmill exercise: a randomized control trial. Neurorehabil Neural Repair, 2012, 26, 85-95.
- Lam, J. M.; Wächter, T.; Globas, C.; Karnath, H.-O. & Luft, A. R. Predictive value and reward in implicit classification learning. Hum Brain Mapp, 2012, doi: 10.1002/hbm.21431, Epub ahead of print.
- Lam, J. M.; Wächter, T.; Globas, C.; Karnath, H.-O. & Luft, A. R. Impaired reward processing and reinforcement learning after stroke. (submitted to Human Brain mapping)

Summary (DE) - Zusammenfassung

In den letzten Jahren verlagerte sich der Fokus der Forschung der Schlaganfallrehabilitation: statt ausschließlich die Funktionsbeeinträchtigungen nach einem Schlaganfall zu kompensieren, wird aktuell vielmehr versucht die hinter der Rehabilitation liegenden Prozesse zu verstehen. Eine wichtige Fragestellung ist hierbei, in wieweit dem Gehirn Hilfestellung gegeben werden kann, um den Erfolg und den Nutzen der Rehabilitationsmaßnahmen zu erhöhen (Nadeau, 2002; Dobkin, 2004). Erkenntnisse über die Plastizität des Gehirns, über Lernmechanismen und die Suche nach Prädiktoren, die die Beeinträchtigung nach einem Schlaganfall und die Wirksamkeit von Therapien vorhersagen können, lenken die Forschung an Rehabilitationsmaßnahmen in eine vielversprechende Richtung.

Studien zu Rehabilitationsprogrammen, wie zum Beispiel dem Laufbandtraining, zeigen positive Gruppeneffekte. Allerdings variiert der Therapieerfolg zwischen den Patienten stark. Das Identifizieren von Prädiktoren, die das Ausmaß des Therapieerfolges vorhersagen können, würde stark dazu beitragen, die erfolgversprechendsten Therapien auszuwählen und diese Therapien individuell anzupassen. Zu diesem Zweck haben wir in der ersten Arbeit die Daten aus zwei randomisiert-kontrollierten Laufband-Studien analysiert. Dabei untersuchten wir den Einfluss von klinischen, demographischen und läsionsbezogenen Parametern (z.B. Ort oder Größe der Läsion) auf die Grundleistung und die Leistungssteigerung der Gehfähigkeit und der Fitness. Patienten mit kleineren sowie Patienten mit linksseitigen Läsionen profitierten am stärksten von der Laufbandtherapie. Des Weiteren wirkte sich ein kürzerer Zeitraum zwischen Schlaganfall und Beginn der Therapie positiv auf den Therapieerfolg aus. Nichtsdestotrotz konnten diese Prädiktoren nur einen Teil der Varianz des Therapieeffektes zwischen den Patienten erklären.

Welche weiteren Faktoren könnten die Therapieeffekte beeinflussen? Im zweiten Teil meiner Dissertation haben wir die Hypothese untersucht, ob es Defizite in Lernprozessen gibt, die zu vermindertem Ansprechen auf Therapien führen. Dies ist besonders interessant, da Mechanismen des Lernens in vielen Rehabilitationstherapien eine wichtige Rolle spielen. Im speziellen betrachteten wir die Verarbeitung von Feedback und Belohnung. Wir untersuchten, ob die Verarbeitung von Feedback bei gesunden Probanden während eines prozeduralen Lernparadigma sich von der bei Schlaganfallpatienten unterscheiden. Diese Unterschiede - wenn vorhanden - können defizitär sein und somit die Lernfähigkeit mindern und den Therapierfolg schmälern.

Beim "Weather Prediction Task" (WPT), einem prozeduralem Lernparadigma, das bereits in früheren Studien verwendet wurde, haben die Probanden die Aufgabe, 14 Kartenkombinationen (eins, zwei oder drei aus vier Karten) der Kategorie "Sonne" oder "Regen" zuzuordnen. Bei gesunden Probanden zeigten wir, dass Kontext und Feedback die Lernkurve positiv beeinflusst: Probanden lernten positiven Kontext ("Sonne") besser und zeigten eine höhere Lernrate bei Kartenkombinationen, bei denen ein positives Feedback folgte. Die fMRI Daten zeigten, dass positives Feedback ("Smiley") im WPT, verglichen zum Feedback im Kontrollparadigma, eine höhere Aktivierung in folgenden Hirnarealen: 1. in den Basalganglien (Putamen, Thalamus, NAcc). Dies bestätigt deren wichtige Rolle im Belohnungslernen. 2. im sensomotorischen Kortex (Motorkortex, Prämotorkor-

tex und somatosensorischer Kortex), welcher in vorherigen Studien nicht mit Belohnungslernen in Verbindung gebracht wurde. Jedoch trägt der sensomotorische Kortex zum motorischen Lernen und zum Erlernen von Gewohnheiten bei, und könnte damit eine wichtige Rolle bei prozeduralen Lernprozessen per se spielen.

Beeinträchtigungen im prozeduralen Lernen könnten das Erholungspotenzial nach einem Schlaganfall reduzieren. In der dritten Studie untersuchten wir, ob eine schlechtere Verarbeitung von Feedback bei Schlaganfallpatienten aus einer Unterbrechung des Belohnungskreislaufes resultiert. Schlaganfallpatienten sind beim Lernen des WPT gegenüber Kontrollprobanden beeinträchtigt. Bildgebende Daten zeigten eine verminderte Aktivierung der Belohnungsareale, die wir zuvor bei den gesunden Probanden nachweisen konnten. Die Läsionsanalyse zeigt, dass es einen Zusammenhang gibt zwischen Lerndefiziten und Läsionen in frontalen Arealen, im Putamen, im Thalamus, im Nucleus caudatus und in der Insula. Dieses Ergebnis, gemeinsam mit den fMRI Daten, weist auf eine beeinträchtigte Verarbeitung von Feedback und Belohnung hin, die aus dysfunktionalen und geschädigten Hirnarealen resultiert.

Die beeinträchtigte Verarbeitung von Feedback und Belohnung bei Schlaganfallpatienten, die im zweiten Teil meiner Dissertation gezeigt wird, könnte bei Rehabilitationsprogrammen wie bei Laufbandstudien eine Rolle spielen. Ob dies als ergänzender Prädiktor bei der Erklärung der Varianz von Therapieeffekten zwischen Patienten herangezogen werden kann, muss in weiteren klinischen Studien untersucht werden.