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Action observation as a tool for neurorehabilitation to moderate motor deficits and aphasia following stroke

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Abstract
The mirror neuron system consists of a set of brain areas capable of matching action observation with action execution. One core feature of the mirror neuron system is the activation of motor areas by action observation alone. This unique capacity of the mirror neuron system to match action perception and action execution stimulated the idea that mirror neuron system plays a crucial role in the understanding of the content of observed actions and may participate in procedural learning. These features bear a high potential for neurorehabilitation of motor deficits and of aphasia following stroke. Since the first articles exploring this principle were published, a growing number of follow-up studies have been conducted in the last decade. Though, the combination of action observation with practice of the observed actions seems to constitute the most powerful approach. In the present review, we present the existing studies analyzing the effects of this neurorehabilitative approach in clinical settings especially in the rehabilitation of stroke associated motor deficits and give a perspective on the ongoing trials by our research group. The data obtained up to date showed significant positive effect of action observation on recovery of motor functions of the upper limbs even in the chronic state after stroke, indicating that our approach might become a new standardized add-on feature of modern neurorehabilitative treatment schemes.

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Research Highlights
(1) The mirror neuron system can be used as basis for neurorehabilitation of motor and aphasic deficits following stroke, due to its unique capacity to process action execution and action perception.
(2) Action observation related mirror neuron system activity can mediate motor learning of new skills or relearning of motor skills lost due to stroke.
(3) The proposed mode of functioning of mirror neuron system is simulation of observed actions. This can constitute a basis for imitation and induction of plasticity in the central nervous system.

INTRODUCTION

Motor deficits are the leading cause of disability following stroke, thus justifying the implementation of many different neurorehabilitative techniques[1-6]. The mechanisms underlying these recovery approaches are multifold, including active relearning strategies and passive processes of lesion adaptation[7]. Most of them are based on the assumption that training the affected limbs would lead to an improvement of the impaired movements and skills, due to plasticity of the central nervous system. However, this perspective has emerged quite recently as stroke rehabilitation has been traditionally focused on either passive facilitation of isolated movements or on the ergotherapy (using alternative behaviours and skills)[8]. The conventional rehabilitational techniques (*e.g.* neurodevelopmental treatment, also named as "Bobath approach") perform assissted motion preparations, tone regularisation and positional controls led by the physiotherapists with a main focus on the avoidance of undesirable false motions[9-11]. These techniques find their basis on the reflex-hierarchical theories; however, they have been criticised as outdated, leading to techniques that increase patients' passivity, only show poor carry-over effects into daily life situations[12] and are expensive and time-consuming[13]. Studies that tested scientific efficiacy are scarce and the available comparative studies show no differences between approaches[9, 14-17].

Among the newer approaches to the treatment of motor deficits after stroke, the so called "bottom-up" techniques are the most common ones. According to Rossetti *et al*[18], these methods consist in the intensive use of the affected limbs to facilitate use-dependend plasticity in the stroke-affected brain. The main assumption behind these new techniques is that the practice of repetitive, active and patient-induced movements of a paretic limb can facilitate the improvement of its functioning, based on reorganization of the central nervous system.

The "bottom-up" metaphor refers to the action path, according to which the movements of the (peripheral) effector stimulate the activity of the central nervous system. The to-be-trained action or movement has to be performed without questioning the quality of performance; this represents a main difference from the classical approaches which expect plastic changes within the central nervous system to be followed by an improvement in movement execution. Rossetti and colleagues[18] concluded that the patients have to relearn the type of movement which they must perform.

There is a growing evidence that these new techniques may be more effective than conventional physiotherapeutic approaches[9, 19], as they require a shorter learning-time of hand, arm movements[19] and provide a better recovery in a shorter amount of time[20]. The effects of repetitive trainings are empirically well-proven[21-25] and stimulated the development of different new effective therapies. The most important example is the: "constraint-induced movement therapy" (CIT; also: "forced-use therapy")[26-28], in which the patient is allowed to use only the affected limb in her/his daily life. This approach relies on the correction of a hypothetical learned non-use of the affected limb and assumes that the preferential use of the unaffected hand leads to a further decline of the motor abilites of the affected one[29]. Further on, the approach involves intensive and task-oriented trainings of the affected limb by mean of shaping techniques in which the complexity of the task raises as far as the motor abilities of the patient increases[30]. In an updated version of this approach, beside the affected (upper) limb the trunk is also trained[31] due to the evidence that patients with hemiparesis often make compensatory movements involving excessive trunk and shoulder movements. Indeed, a restriction of trunk movements during therapeutic reaching tasks determine increase of arm joint ranges and improvement in interjoint coordination[31]. A new trial addressing this issue is currently performed which employes a blinded study design[32].

Two further approaches using bottom-up techniques are the motor relearning programme[33], and the repetitive arm training[34], both using systematic and repetitive effector stimulation to induce reorganizational processes. These neurorehabilitative trainings have obtained the best rehabilitative outcomes so far, better than the traditional physiotherapy approaches.

Besides the bottom-up treatment schemes, new "top-down" based approaches are trying to stimulate the brain in a more direct manner in order to elicit plasticity effects. Neuronal stimulations different from active and passive practice of the affected limb are used here. Indeed, several different trainings have been invented in the last two decades, all including action imagination or observation: The earliest evaluated techniques in this field use "mental techniques" to induce representational modifications within the cerebral motor areas - for example: motor imagery or "thinking of performing motor acts"[35]. This method has already been used for decades in the field of sport demonstrating that when combined with physical training, motor imagery is able to ameliorate the target motor skills[36]. Results concerning post-stroke treatment using motor imagery alone so far showed positive effects, although they were less pronounced than the effects of conventional physiotherapy[37]. However, the combination of both recent top-down and classical bottom-up techniques showed a clear additional positive effect over conventional rehabilitation treatment[38-39].

THE TREATMENT OF POST STROKE APHASIA AS A PARALLEL DEVELOPMENT TO PHYSIOTHERAPEUTIC APPROACHES

Neurophysiological evidence suggests a significant interaction between brain areas involved in the language functions and areas responsible for motor planning and execution as well as interpretation, comprehension and perception of observed actions[40-41]. The link between the language system and the motor system is also supported by the clinical observation that stroke-related motor disabilities are often present in combination with aphasic symptoms and mostly after lesions of the left hemisphere. Indeed, the so called "post-stroke aphasia" (PSA) is defined as a condition of partial or complete loss of the language function after vascular damage[42-43]. Due to the lateralization of the most language-related areas, aphasic symptoms most often occur after left hemispheric damage. Aphasic symptoms are among the common symptoms that become manifest following a stroke[41-45], and have been often observed to recover spontaneously [46-48]. Within neurorehabilitative treatments of the combined paretic and aphasic symptoms, aphasic patients are often unable to understand their therapist's instructions on performing manual tasks[49]. In these cases, fostering the treatment of aphasia is needed in order to improve communication, for example by mean of gesture training. There is evidence that the intact hemisphere may take over lost functions of the affected hemisphere[43, 50-51] as it is believed to be also the case in motor rehabilitation[52]. Also, according to Oliveira and Damasceno[53], one may hypothesize a tendency for language recovery to accompany motor recovery. Along this line, it could be demonstrated that the best predictor for the severity of post-stoke aphasia may be the size of infarction. Although one may not find the strict subdivision of the available PSA related treatments in top-down and bottom-up approaches, it seems evidential that – analogue to the treatment of post-stroke motor disabilities – a repetitive intensive training allows the highest efficacy beside the effects of pharmacotherapy[54-56]. Among these approaches, a constraint induced therapy of PSA[57] has been evaluated to be very effective even in chronic states of aphasia[58-59]. Within this therapeutic scheme, principles of the constrained-induced therapy of motor disabilities have been transformed for the use of language. As it is known that aphasic patients often use very short sentences or gestures for communication as a compensatory strategy, the therapeutic approach tries to force the use of more fluent speech and the restriction of gestures. Along this line, the targeted functions are addressed by the forced-use of speech in small steps during a shaping process and are accompanied by reinforcement strategies as known from behavioral sciences[60]. Further on, the therapy is administered in a concentrated, massed-practice fashion similar to the physiotherapeutic focused forced-use therapy and provided evidence to be similarly effective[59]. In parallel to the treatment of paretic limbs, the forced-use therapy of aphasia is believed to allow for facilitated take over of lost function by the language-related areas of the intact hemisphere[61]."

MOTOR OBSERVATION IN NEUROREHABILITATION

Another, top-down Another, top-down technique capable of stimulating motor areas is action observation[28]. Here, the trainee has to watch carefully pre-recorded or actually performed movements and thereafter to imitate them. It has been demonstrated that the mere observation of motor actions performed by an actor activates the corresponding motor representations in the brain of an observer[62]. Although the positive effects of motor observations on the learning of behaviors have been known for a decade[63], the neurorehabilitative use of this approach is quire recent. The theoretical frame for this therapeutic approach lies in the discovery of the so called *mirror neurons* and their functional abilities.

In comparison to motor imagery, the action observation technique bears several advantages. Action observation provides well controllable and quantifiable amount of stimulation. Motor imagery, instead, is not really controllable at all because one can only rely on the report of patients. While in action observation, the amount of visually presented actions can be well defined, the ability to imagine movements varies considerably from individual to individual and can be assessed only indirectly by off-line tests. Neuroimaging studies provide further evidence that action observation reliably activates the brain areas coding actions in a bilateral manner, whereas the activation caused by motor imagery is much more variable and lateralized.

THE MIRROR NEURON SYSTEM

Since the mid-19th century, it is known that the focused observation of salient movements with a certain effector can cause activation of muscles in the related effector of the observer (*i.e*., the Carpenter effect). Moreover, since the beginning of the seventies of the last century, evidence has been provided that observation of motor prototypes can induce motor learning effects in the observer[63]. Facilitatory effects of observed actions on the performance of related actions in the observer were investigated by experimental psychologists in the second half of the 20th century.

A physiological correlate for the facilitatory effects of action observation on action execution has been found in monkey[64-66]. Indeed, certain motor neurons become active not only during the performance of a certain movement, but also when the same action was observed. This mirroring of the observed actions with the self-performed, congruent ones was the motivation for the name: "mirror neurons"[64-67]. Neurons with such properties can be found in several areas of the monkey brain. It is currently assumed that the nerve cells in the superior temporal cortex, in the anterior intraparietal area (AIP) of the inferior parietal cortex and in the ventral premotor cortex would form a functional system: the so-called motor "mirror neuron system" (Figure 1).

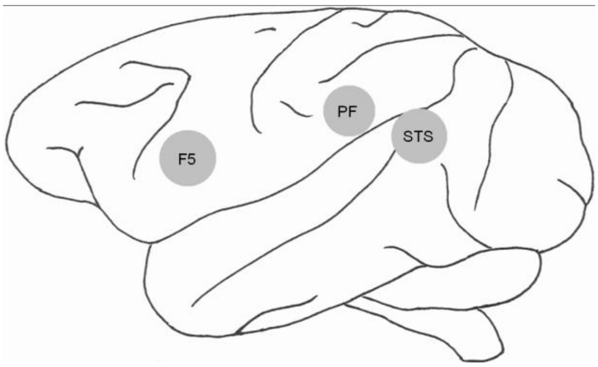

Figure 1 Parietal and premotor areas constituting the macaque's mirror neuron system[104].

F5: ventral premotor cortex; PF: inferior parietal cortex; STS : sulcus temporalis superior.

THE HUMAN MIRROR NEURON SYSTEM

Results from neuro-physiological, neuro-psychological, learning-psychological and neuroimaging studies provided strong hints towards the existence of a human mirror neuron system[68-69]. Neuroimaging studies could especially demonstrate a high correlation between directly recorded cell activations and activations seen in functional Magnetic Resonance Imaging (fMRI) measurements[68]; therefore neural activations found in relation to action observation in the homologue areas of the monkey mirror neuron system are very likely to represent activation of the human mirror neuron system. As ethical reasons do not permit human nerve cell recordings for pure experimental scientific purposes, direct proofs of human mirror neurons were not available until recently. Quite recently, during diagnostic recordings with intracranial electrodes, neuronal populations reacting to action observation and action performance were observed in the human brain[70]. These findings provide most probably the long overdue direct proof of a human mirror neuron system. They also provide confirmation for the numerous results obtained with imaging techniques as well as using the transcranial magnetic stimulation (TMS).

In general, the posterior part of the inferior frontal gyrus, including the Broca's area and the ventral part of the lower precentral gyrus, as well as the supramarginal cortex and the rostral part of the inferior parietal lobe are assumed to constitute the main elements of the human motor mirror neuron system[71] with additional cells having similar characteristics in the left inferior frontal lobe and the posterior temporal lobe[72]. The latter nerve cells can be activated by hearing sounds caused by typical actions, as for example the shredding of paper, and by the performance of the same actions by the listener[73]. Many recent studies were able to identify these acoustic mirror neurons with different techniques, such as TMS[74-75]; event-related potentials in EEG[76]; as well as functional MRI (fMRI)[72, 77-78]. In general, the direct and indirect findings in humans suggest that the human mirror neuron system may be larger than monkey mirror neuron system, thus including somatosensory areas being somatotopicaly organized[62, 70, 79].

The main hypothesis about the mechanisms of action of the mirror neuron system postulates an internal imitation of the perceived actions. Along these lines, action observation is supposed to induce a re-enactment of similar actions stored in human brains[62, 71, 80] possibly by inducing a simulation of the ongoing actions[81].

Using an internal simulation, we can re-activate action representations previously stored in our motor memory, which can help us to understand the content of the observed actions and support motor learning. It is therefore likely that action observation leads to organisational changes in the brain[82] and may participate, *via* the mirror neuron system, in the learning of motor skills[83] or even in language acquisition and comprehension[84-87]. One prominent example is the learning of new thumb movements facilitated by action observation[39, 88-89]. It could also be demonstrated that the properties of the human mirror neurons are not fixed; but they develop through sensorimotor learning, for example, in the context of social interaction[90]. These findings support the idea of a significant role of the mirror neuron system in memory formation, for example in the human motor learning.

REHABILITATIVE RESEARCH BASED ON MIRROR NEURON SYSTEM CONCEPTS

As Buccino *et al* [91] reviewed, the capacity of the mirror neuron system to take part and control the imitation and the learning of new motor actions through observation can be utilized in the neurorehabilitation of acquired motor deficits. Most of the physiotherapeutic approaches address compensatory mechanisms that allow the patients to maintain their motor potential or to provide functional recovery on the basis of the remaining motor abilities. The mirror neuron system is supposed to actively participate in the rehabilitation process. Along this line, Buccino and colleagues[91] propose four possible mechanisms of involvement of mirror neuron system in reestablishing previously learned motor skills affected by stroke: (i). The mirror neuron system can be activated by actions presented in different modalities (visual, acoustic, tactile). (ii) Mirror neuron system has a direct influence on activation of corticospinal pathways. (iii) Mirror neuron system can activate previously learned, ecologically valid movements. Furthermore, Buccino *et al*[91] emphasized the advantage of imitation in rehabilitation which allows for implementation of activities of daily living into the treatment and to use real actions instead of fragmented actions as in traditional physiotherapy. (vi) Mirror neuron system is supposed to participate in motor imagery as well as in imitation. Both processes may facilitate each other and ameliorate recovery of function.

Despite in the advertisement of a clear cut physiological background for the action observation treatment[91-92], only few up to date studies addressed this experimental and clinical question and tested the effects of action observation in neurorehabilitative treatments.

One of the first therapies that have been associated with the function of the mirror neuron system is the so called "mirror therapy". In this therapy, the patient sits in front of a mirror at a cetain angle so that only the stroke-unaffected side of the body is reflected. The task is to perform bilateral actions, while the patient observes the healthy limb reflected in the mirror. In this situation, a strong illusion occurs bringing up the sensation that the affected limb is moving in a normal, unaffected way. Originally developed for the treatment of phantom pain[93], with the theoretical background of allowing the correction of false internal body representations, the concept also demonstrates to be effective in the treatment of stroke related hemiparesis[94]. However, although it would be reasonable to deduce the participation of the mirror neuron system in the effects of therapy, neuroimaging studies found so far no evidence for an involvement of mirror neuron system in mirror therapy[95-96]. Neuroimaging studies could, however, demonstrate that mirror therapy is inducing activation of the contalesional hemisphere, which is probably one of the reasons for the effectiveness of this form of treatment[97-99]. The existence of a cross-facilitatory drive from the intact to the damaged hemisphere may increase excitability in the mirror neurons and the homologous motor pathways of the paretic limb, thus enhancing their readiness and facilitating recovery of their function. However, an empirical study addressing this question still asks to be implemented in future.

A related form of therapy combining the mirror therapy with an intensive training of mental imagery has shown very promising results in a pilot trial[100]. Interestingly, this training used videos of actions to be observed, first and then imagined. Thus, this training is most probably also activating mirror neuron system.

Pomeroy *et al* [101] are the first to hypothesize a therapeutic scheme exclusively based on mirror neuron system. They propose the combination of action observation with active imitation using the affected limb, believing that the most important component would be the intention beside the action observation. This would allow for the preparation of the action execution system for the eventual active action performance. The identification of brain areas responsible for the intention to imitate observed actions may allow for a prospective diagnosis of a successful participation in this therapy.

USING THE MIRROR NEURON SYSTEM FOR MOTOR NEUROREHABILITATION: A PILOT STUDY

Our group was one of the first to analyze the rehabilitative properties of the mirror neuron system in form of a pilot clinical trial[102-105]. We were indeed able to provide the first evidence that the mirror neuron system have the potential to improve rehabilitation of motor deficits after stroke.

In this pilot study, we used a design with one treatment group and one control group at a post stroke chronic stage. Eight patients were assigned to each group after giving their informed consent. Fifteen patients (four females) with a confirmed diagnosis of a first ever ischemic stroke in the territory of the medial cerebral artery, sustained more than 6 months prior to participation. One further female patient was recruited with the diagnosis of a traumatic brain injury, also occurred more than 6 months prior to recruitment. All patients had a moderate paresis of the contralesional arm, as assessed by standard functional scales (Wolf Motor Function Test WMFT[106], Frenchay Arm Test FAT[107], MRC-Index[108]).

The experimental condition consisted in watching video clips containing daily activities and soon afterwards imitating these activities with the paretic limb using identical training objects. Since in our studies, we used action observation provided by video clips, we called the treatment "Videotherapy". According to other neurorehabilitative top-down approaches, like motor imagery, it is well known that the mental training alone is by far not as effective as in combination with motor exercise[38]. Therefore, the combination of action observation and motor exercise of the observed actions was the core feature of the videotherapy. The control condition matched the treatment condition, except for watching slideshows of geometric symbols instead of daily motor activities. Indeed, geometric symbols do not have as strong effects on the motor system as action observation[104].

Statistical analyses showed a highly significant improvement in all the experimental group members during the course of treatment as evidenced by both objective (WMFT, FAT) scales on a statistical significance $P < 0.01$ and on the subjective (stroke impact scale[109]) on a statistical significance $P < 0.05$. The control group of patients did not show noticeable improvement during the course of the training ($P > 0.1$). The direct comparison between the two groups confirmed the better improvement of the motor skills in the treatment compared to the control group. The second level analysis was based on the calculation of the differences between post-test and pre-test measurements for each group: comparisons between the experimental and the control group showed a significant difference at a significance level below 0.001 for all measures, except for the result of the WMFT comparison which just reached the lowest level of significance ($P < 0.05$). The differences between the delta-calculations of the experimental and the control groups showed differences in favor of the experimental group in all scales (FAT: 1.875 points, WMFT: −2.872 seconds, SIS: 17.6 points). Additionally, the effects of action observation therapy on the reorganization of the motor system were monitored by fMRI using a therapy unrelated sensorimotor task containing object manipulation[102-105]. The major result of the fMRI study was revealed by direct comparison of the changes in neural activation, during the treatment, between the experimental and the control groups. Indeed, we demonstrated that the positive effect of our treatment is related to an increase in activation in the bilateral ventral premotor cortex, bilateral superior temporal gyrus, supplementary motor area and contralateral supramarginal gyrus. Our results provide evidence that action observation has a positive additional impact on the recovery of motor functions after stroke: it stimulates the reactivation of those motor areas which contain the action observation/execution matching system.

Our results have been confirmed by other groups. For example, Franceschini *et al* [110] showed that a significant effect of action observation followed by action execution, in an approach quite similar to ours, was highlighted by functional scales and demonstrated to be still present at a 2-month follow-up assessment. However, the lack of a control condition is a serious drawback of this study. More recently, Franceschini *et al*[111] performed a second study using the controlled version of the same design[102-104]: 79 non-chronic patients conducted either action-execution training or a control condition. In this control condition, static images of objects were shown combined with an attentional task and combined with physical execution of the experimental tasks. Experimental and control treatments lasted for 20 working days with two sessions lasting 15-minute per day. Patient's motor abilities were assessed by functional scores. Results showed a significant improvement in the functional motor abilities in the patients from both groups. However, the assessment of the Box-and-Block-Test[112], *i.e.* a functional test to evaluate the gross manual dexterity, showed a statistically significant effect in favour of the experimental group. While interpreting the results of this study, a few factors have to be kept in mind. First of all, the recovery of patients may be confounded with spontaneous recovery, a fact well known at the early stage after stroke[113]. Second, during the trial, the patients were allowed to participate in not further defined outpatient treatment with 3 to 5 sessions a week lasting for 1 hour. This relatively long outpatient treatment stands in contrast with the relatively short experimental treatment and very likely biased the results of the experimental treatment. Further on, the use of object pictures in the control condition may have elicited activation of the so called canonical neurons, a group of neurons localized in the same areas as the mirror neuron system[71]. The potential activation of the canonical neurons could indeed have ameliorated the effects of treatment in the control group. Thus, this activation of the canonical neurons could have diminished the significance of the main experimental question of a study from Franceschini *et al* [111].

A very well controlled TMS study was conducted by Celnik *et al* [114] on stroke patients: it could nevertheless demonstrate clearly positive effects of combined action observation and action execution on formation of motor memory. In conditions with isolated action execution and with observation of an incongruent motor action combined with action execution showed no positive results. These results indicate that the observation of a congruent action in association with physical training can enhance the effects of motor training after stroke. A similar result was also obtained by Sgandurra *et al* [115] for the rehabilitation of hemiplegic cerebral palsy. This disease is defined as a group of motor disorders leading to only limited motor activity and a wide variety of accompanied psychomotor, sensational and social disorders. It is supposed to be caused by non-progressive disturbances during the developmental phase of the fetal or infant brain[116]. Sgandurra designed training for upper-limb paresis in cerebral palsy affected children by using action observations matching daily activities of children. Although results have not been published until printing of this review, their prerequisites are promising.

During the preparation of a major clinical trial, our group performed two further pilot studies using the action observation therapy. Here, the feasibility of an outpatient-conducted videotherapy for stroke patients was tested in a small study conducted for a thesis[117]. Patients practiced at home for 1 hour on 20 consecutive weekdays; while the control group patients received written instructions to perform the same hand actions for 1 hour a day. Once a week, patients' activity was checked by phone. Any additional training they received outside the protocol, they documented in a diary. There was an excellent compliance in both groups without any dropouts and the participating patients appreciated being included in the protocol and controlled after their training. Comparisons in scales for the quantity of movement (investigated with the Motor Activity Log[118]) across the groups revealed a significant improvement in the experimental group, but not the control group. Further on, the assessment of the motor abilities *via* the WMFT demonstrated a significant improvement concerning velocity of movements ($Z = -2.80$, $P = 0.002$, $d = 1.21$). The study confirmed that home based videotherapy shows a high acceptance by the patients and may lead towards improvements in mobility of the trained paretic limbs. Another thesis was submitted to the Department of Psychology in Konstanz[119-120], investigating age-related effects of the blood oxygen level dependency signal in the motor system on healthy subjects in one experimental and one control group. The primary motor cortex and some motor association cortices showed age-related increases of the blood oxygen level dependency signal which was interpreted as a form of compensation: We assume that these changes represent adaptive plasticity within the motor network in order to maintain performance in the face of age-related changes in the brain. Interestingly, the mirror neuron system did not show any age-related changes. This is an important prerequisite for application and evaluation of videotherapy in stroke patients with the use of fMRI. The same thesis tried to optimize a paradigm for the investigation of stroke patients and to precisely delineate the difference between action observation and action imagery[121].

In a recent fMRI study, the cortical processes associated with imagery of wrist movements in patients with severe hemiparesis were investigated in both hands of the patients in comparison to a healthy control group. Healthy subjects demonstrated contralateral control during the imagery condition, whereas subjects with stroke displayed primarily contralateral activation in S1 but ipsilateral in M1 and supplementary motor area. The percentage change in signal intensity was greater in the ipsilateral hemisphere in subjects with stroke than in the ipsilateral hemisphere in healthy subjects during the imagine condition. Additionally, subjects with self-reported low ability to imagine displayed no difference in activation compared to those with high imagery ability[122]. In a recent TMS study, the activation of M1 related to motor imagery has been investigated in patients with hemiparetic stroke[123]. Patients are reported to be able to imagine movements with either hand, despite no measurable facilitation of motor evoked potential (MEPs) in the stroke-affected hand. In left hemisphere patients, MEPs were facilitated in the left hand during imagery of the right hand and both hands together[123]. In right hemisphere patients, motor imagery did not facilitate MEPs in either hand. The conclusion of the both studies is that motor imagery does not appear to facilitate the ipsilesional M1 after the stroke. The crucial question in this context is whether action observation has a better impact on activation of motor related areas in hemiparetic stroke patients. We investigated stroke patients using fMRI and the observation of simple, object-related actions. Evaluation of the data in eight right-hemispheric and eight left-hemispheric stroke patients revealed that both hemispheres are activated by action observation: the affected hemisphere as well as the non-affected one[121, 124]. This result suggests that application of observation as neurorehabilitative tool might have some advantage over motor imagery.

In a further ongoing trial[125], our group is relating sleep parameters to the therapeutic success of action observation therapy, since motor recovery after stroke is dependent on multiple factors, including sleep. Changes in sleep EEG patterns after hemispheric stroke have been documented in several studies[126-127], and sleep efficiency, as well as slow-wave sleep and rapid eye movement (REM) sleep, seem to be reduced in patients with acute hemispheric stroke[127]. Sleep efficiency[128], preserved spindle activity[127] and amount of REM sleep[129] in the acute phase of stroke have been shown to be associated with favourable outcome. There is growing scientific interest on how sleep disturbances affect recovery of cognitive and motor functions[130], but the exact impact of sleep disturbance on the process of recovery is still an open question. Because sleep has an important impact on motor learning and re-learning, interactions between sleep disturbances and motor recovery can be expected. To examine this in patients, we assess their sleep parameters to evaluate possible interactions to the videotherapy. This would allow to pre-estimate possible beneficial outcome of the videotherapy in patients on the basis of their sleep architecture. In a controlled study with parallel-group design, inpatients with early chronic stroke and arm paresis will perform the videotherapy, a comparable group of inpatients will perform the placebo condition with physical exercises and geometric slideshows as described in previous reports[102-105] (see above) (non-video-group). We expect that the treatment group (video) will show the best recovery in comparison to the control exercise group (non-video) as assessed by objective standardised motor scales (WMFT and FAT) as well as in standardized subjective self assessment (SIS). Further on, we will examine patients' sleep architecture with polysomnography. Possible interactions between sleep disturbances and mood or motivation will be assessed with psychological scales. We expect that patients without sleep disturbances will benefit most from the videotherapy.

USING THE MIRROR NEURON SYSTEM FOR NEUROREHABILITATION OF POST-STROKE APHASIA

Regarding the coincidence that the Broca's area - traditionally associated with the production of speech and language[131] - is closely co-localized with the ventral premotor site of the mirror neuron system[71], it is not surprising that a link between action and language processing has been proposed. In this context, the idea has been put forward that mirror neuron system might play an important role in the recovery of language functions, which is similar to the one already described for the motor system. As mentioned above, mirror neuron system may play an important role in motor learning *via* action observation and therefore may support re-learning of lost language skills after stroke.

A new form of therapeutic approach of language deficits after stroke (IMITATE) was presented by Lee *et al* [132], using intensive action observation followed by imitation as therapeutic intervention. The time schedule of IMITATE consists of 9-hour lasting computer aided training per week for a period of 6 weeks. The intervention consists of audio-visual presentations of words and phrases followed by their oral repetition. Further on, only ecologically valid terms and phrases are used to allow the best possible activation of the mirror neuron system. The training supports incremental learning in a shaping process adapted to the patient's progress in the training: The therapy starts with the imitation of monosyllabic words and continues with disyllabic words, simple phrases containing two or three words. The variability is provided in form of changing speakers presenting the stimulus throughout the training and in form of the complexity of the stimuli presented. The so far reported preliminary results[132] are promising; however, a thorough evaluation of the programme has to be made.

In a recent study, a pronounced functional connectivity between the language and action coding brain areas was demonstrated in the process of recovery of aphasia[133]. Patients recovering from aphasia were asked to read aloud while Motor Evoked Potentials were elicited by TMS. Reading aloud enhanced excitability of the right hemispheric hand motor cortex, while phonation had no effect on excitability of the motor cortex. In contrast, in healthy control subjects, an increased excitability of their left hemispheric hand motor system could be found. These results suggest a functional connectivity between brain areas for language production and areas for coding of hand movements, that is, another indication of the mediating role of the mirror neuron system between the two cognitive functions. Further on, these results emphasize the facilitative effects of the intact hemisphere in the recovery from aphasia[43, 51].

CONCLUSION

Taken together, our studies regarding controlled interventions on patients let us assume the feasibility and the effectiveness of a training course based on action observation and physical imitation. It is highly probable that future studies will reveal further potential of the mirror neuron system in neurorehabilitation; our ongoing studies as well as other research groups studies might be implemented as an add-on physiotherapeutic practice in motor as well as in aphasia treatment. As at present there is no shared rationale for selecting the appropriate physiotherapeutic regime in a particular individual patient, our studies on how and where different therapeutic strategies act in the brain will optimize the rational basis for applying different therapies including the videotherapy. This way, the sleep architecture of the individual patient could be used as a possible marker to predict the probable efficacy of the treatment.

For all these reasons, future results of studies on the use of action observation in neurorehabilitation are of great interest for the community of neurologists and physiotherapists, far beyond the current research setting.

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