Anatomy of brain lesions after stroke predicts effectiveness of mirror therapy

Farsin Hamzei1,2 | Gabriele Erath3 | Ursula Kücking3 | Cornelius Weiller3 | Michel Rijntjes3

1Section of Neurological Rehabilitation, Hans Berger Clinic of Neurology, Department of Neurology, Jena University Hospital, Jena, Germany
2Department of Neurology, Moritz Klinik, Bad Klosterlausnitz, Germany
3Department of Neurology, Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany

Correspondence
Farsin Hamzei, Department of Neurology, Moritz Klinik, Hermann-Sachse Str. 46, 07639 Bad Klosterlausnitz, Germany. Email: farsin.hamzei@moritz-klinik.de

Abstract
To improve clinical outcome, one longstanding goal in treating stroke patients has been an individual therapy based on functional and anatomical knowledge of the single patient. Therefore, in this study brain imaging of 36 chronic stroke patients was analyzed to identify parameters predicting clinical recovery. T1-weighted MRI was acquired to assess the lesion; functional MRI was used to visualize existing resources; DTI for the integrity of the corticospinal tract (CST) and long association tracts. These data were related to the clinical course. All patients were treated intensively with the mirror therapy (MT) only. After the training period, we analyzed which patient's feature would predict a beneficial course. Patients as a group improved after MT, but according to the fMRI activation of primary sensorimotor cortex (SMC), they could be divided in two groups with very diverging clinical outcome: those with ipsilesional SMC activation showed a noticeable increase of clinical scores, accompanied with ipsilesional activation in the frontal projection areas of the dorsal and ventral streams during action observation in fMRI. Those with contralesional SMC activation had lesions affecting both the dorsal and ventral stream and did not benefit from MT. The outcome for this therapy was not related to affection of CST. This study demonstrates that only in patients in which dorsal and ventral streams are not affected and therefore an interaction between these streams in post- and prerolandic regions is possible, MT can induce clinical improvement. Consequently, knowledge of the anatomical lesion can predict the beneficial course of MT.

KEYWORDS
brain plasticity, dual loop model, fMRI, mirror therapy, stroke rehabilitation

Abbreviations: AF, arcuate fasciculus; ANOVA, analysis of variance; AO, action observation; CST, corticospinal tract; dPMC, dorsal premotor cortex; DTI, diffusion tensor imaging; EmC, fasciculus extreme capsule; FA, fractional anisotropy; FDR, false discovery rate; fMRI, functional magnet resonance tomography; HS, hemisphere; IFG, Inferior frontal gyrus; IMI, imitation; IPL, inferior parietal cortex; MNS, mirror neuron system; MT, mirror therapy; PM, passive wrist movement condition; SLF, fasciculus longitudinalis superior; SMC, primary sensorimotor cortex; VLSM, voxel-based lesion-symptom mapping; vPMC, ventral premotor cortex; WMFT, Wolf Motor Function Test.

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1  INTRODUCTION

How can we use scientific neuroimaging to improve the care of patients effectively? So far, therapeutic applications of human scientific brain imaging have been scarce. For example, after stroke, the effect sizes of neurorehabilitation are small in group studies (Ward, Payne, Caro, Heuschenmann, & Kolominsky-Rabas, 2005). This may be due to inappropriate selection. Thus, a longstanding goal has been an individualized therapeutic approach based on functional and anatomical knowledge of the one patient in front of us (Ingemanson et al., 2019; Laible et al., 2012; Nouri & Cramer, 2011; Stinear et al., 2007). One way of dealing with this problem is to understand what anatomical requirements specific treatments pose and use this information to assess whether a lesion affecting part of a network will predict if an individual patient will benefit from a certain therapy. Mirror therapy (MT) can be effective in stroke rehabilitation and simultaneously has a clear hypothesis about the underlying mechanisms, based on the activation of specific brain regions required to perform MT in healthy subjects (Hamzei, Lappchen, et al., 2012).

In MT, stroke patients train the unaffected hand while observing the hand in a mirror perpendicular to their body, experiencing the illusion that the affected hand is moved. Group studies show that MT is effective for improving hand function after stroke (Dohle et al., 2009; Lim, Lee, Yoo, Yun, & Hwang, 2016; Thieme, Mehrholz, Pohl, Behrens, & Dohle, 2012; Yavuzer et al., 2008). However, not all patients profit from this therapy and so far, no parameter has been identified to predict which patient is suitable for this therapy. Since the functional and anatomical basis of MT in healthy subjects are well studied, this therapy seems to be a good candidate to investigate whether knowledge how a lesion affecting the anatomical and functional organization of the motor network can predict the clinical benefit of this therapy in individual stroke patients.

Considering the dual loop model, a dorsal and ventral stream connect post- and prerolandic regions. The dorsal stream is further subdivided into a dorso-dorsal and into a ventro-dorsal stream (Rizzolatti & Matelli, 2003). The dorso-dorsal stream connecting superior parietal lobe and dorsal premotor cortex (dPMC) is used for online sensorimotor and visuomotor control for variable movement parameters (Rizzolatti, Cattaneo, Fabbri-Destro, & Rozzi, 2014). In the ventro-dorsal stream, connecting inferior parietal cortex (IPL) and ventral premotor cortex (vPMC) as well as BA 44, blueprints for parameters of (over-)learned movements are stored (Hamzei et al., 2016; Rijntjes et al., 1999), as well as stable movement parameters connected with the use of known tools (“affordances”; Binkofski & Buxbaum, 2013; Martin et al., 2016; Martin et al., 2017; Sakreida et al., 2016). The ventral stream, collecting fiber tracts from different postrolandic regions, running through the extreme capsule (EmC) and projecting on BA 45, connects areas responsible for structural analysis and conceptual meaning of the sequential input provided by the dorso-dorsal and ventro-dorsal stream (Rijntjes, Weiller, Bormann, & Musso, 2012; Weiller, Bormann, Saur, Musso, & Rijntjes, 2011).

In a previous study in healthy subjects, MT of the right hand (20 min/day during 4 days) led to functional improvement of the untrained left hand (Hamzei, Lappchen, et al., 2012). fMRI revealed that MT activates networks among others the mirror neuron system (MNS), based on the ventro-dorsal stream. In a further study, the activation of the ventro-dorsal stream during action observation was demonstrated to be closely connected to involvement of the ventral stream, showing that action observation is accompanied by understanding the observed action (Hamzei et al., 2016). If “understanding” of the observed action is also a prerequisite for the effectiveness of MT (which gives the illusion that the affected hand is moved during action observation), is so far unknown.

The question therefore is whether the effectiveness of mirror therapy in stroke patients depends on the integrity of either the ventro-dorsal stream or the ventral stream of the affected hemisphere (HS), or both.

In the present study, we offered mirror therapy to chronic stroke patients with hemiparesis and correlated clinical improvement with lesion localization. To investigate the mechanisms leading to clinical improvement, similar to the previous study on MT in healthy subjects (Hamzei, Lappchen, et al., 2012), we looked at activation patterns in fMRI before and after therapy during action observation (AO) and imitation (IMI) of video sequences. Whatever networks are addressed by MT, reorganization should ultimately encompass the primary sensorimotor cortex (SMC) contralateral to the affected hand. Therefore, passive movement, which leads to activation of the SMC (Weiller et al., 1996) and is independent from performance, was investigated before and after MT. Also, since recovery from motor stroke depends strongly on the amount of lesion to the corticospinal tract (Stinear et al., 2007), its integrity was investigated with DTI. Considering previous work that MT is associated with activation of dorsal and ventral streams we hypothesized that affection of these networks due to stroke would be a limiting factor for a beneficial course of MT. In that case, the related stroke lesion would be a predictive value for MT.

2  MATERIALS AND METHODS

2.1  Patients

From 36 recruited right-handed patients 33 patients completed the study (see Table 1; three patients were excluded because of head movement during fMRI). Inclusion criteria consisted of at least minimal visually detectable active finger or hand movement and a maximum score of 3.0 of the
affected arm on the Motor Activity Log (Taub et al., 1993) to exclude patients whose motor functioning was too close to a ceiling for them to benefit from the training program. Stroke occurrence should be more than 1 year before the first interview. Exclusion criteria were haemodynamically relevant intra- or extracranial artery stenosis in Doppler ultrasound, which may alter the blood-oxygenation level dependent response (Hamzei, Knab, Weiller, & Rother, 2003); cognitive impairments or aphasia that prohibit the following of study instructions; attention deficits (i.e., visual neglect); serious uncontrolled medical problems; medications known to alter central nervous system excitability (such as selective serotonin reuptake inhibitors); metallic implants (like pace maker); epilepsy and spasticity (modified Ashworth scale >2). Written informed consent was obtained from all patients in accordance with the Declaration of Helsinki. The study was approved by the local ethics committee.

2.2 | Clinical assessments

At least 3 months prior to the start of the training program, eligibility for the experiment was assessed. If patients met the inclusion criteria, the project’s procedures were explained to them and written informed consent was obtained. At this time point of recruitment, physiotherapists evaluated the Wolf Motor Function Test (WMFT) with the Functional Ability (WMFT-FA), and number of seconds needed for these tests (WMFT-sec), measured with a stop-watch (Taub et al., 1993; Wolf, Lecraw, Barton, & Jann, 1989).

The Wolf Motor Function Test (WMFT) is a test of motor ability that evaluates the speed (WMFT-sec) and the quality of movement (functional ability; WMFT-FA) of 15 timed tasks and two strength tasks. For WMFT-FA, a 6-point functional ability scale (0 = does not attempt, to 5 = normal movement) is used. For WMFT-sec, 120 s was the maximum time permitted to complete an item.

The timed tasks were as follows: moving the forearm to tabletop starting with the arm in the lap perpendicular and parallel to the table, moving the forearm to the top of a box 26 cm in height placed on the table, and the same task for the hand only. Elbow extension for 40 cm while sitting parallel to the table, with and without weight, reaching to retrieve the weight by bringing it toward the body using elbow and wrist flexion, lifting a can to mouth, lifting a pencil and paper clip, stacking three checkers, turning over three index cards, and turning a key in a lock while sitting in front of a table, folding a towel, standing in front of the table and lifting a basket containing weight and moving it from one table to another using trunk rotation.

The two strength tasks include forward flexion of the shoulder in a seated position to the top of a box placed on the table, with a weight strapped to the forearm, as well as a dynamometer grip strength for three seconds with the elbow bent to 90°.

Each timed task consisted of a single trial while the weight-to-box was repeated until maximum weight lift was achieved. The dynamometric task was averaged over three trials.

To ensure that patients were in a stable clinical stadium, patients were excluded if these tests evaluated at a time point “baseline” (the beginning of the training program) were better or worse than the same tests at the time point of recruitment (at least 3 months before; for WMFT-sec a difference of ±1 s was allowed).
The training lasted 4 weeks with daily training on all working days, starting on a Monday (baseline) and finishing on day 25. The WMFT (WMFT-FA and WMFT-sec) was evaluated at baseline, at day 7 (d7), day 14 (d14), and day 21 (d21) after baseline, always on a Monday at 09:00 a.m. The last test session (post) was at day 25 at the end of the training program on a Friday at 09:00 a.m. All tests were performed by physiotherapists who were not involved in the training program. Within the whole duration of the study, patients did not have access to their weekly occupational and physical therapy.

Since we were interested in the relative change of recovery, for each patient the percent change to baseline of WMFT-FA and of WMFT-sec was evaluated. Thereafter, for each patient an average percent WMFT was calculated (%WMFT = (%WMFT-FA + %WMFT-sec)/2). For all further analysis, this average percent WMFT (WMFT) was used. In order to test clinical efficacy, we applied an ANOVA with time as an independent variable. Threshold for significance was set at p < .05, corrected for multiple comparisons (Bonferroni correction). A paired t test was also performed between each testing day (day 7, 14, 21, and 25) compared with baseline (level of significance was set p < .05, corrected for multiple comparisons, Bonferroni correction).

### 2.3 Training program

The training program of MT started at the day of the baseline testing and lasted 4 weeks. The whole training time in the four-week training program was 1,800 min. To take into account that repetitive training of task-specific practice is highly effective, the daily MT program was implemented in transitive training sessions which were divided into repetitive tasks of three minutes (Hamzei, Lappchen, et al., 2012; Lappchen et al., 2015, 2012). Within the daily training session of 120 min, each task was repeated twice (thus, for each day 20 tasks were trained). The number of successful performances within an exercise of three minutes was counted and recorded. With an instructor sitting beside them, patients were encouraged to execute the exercises quickly and to remain focused on the task while continually looking in the mirror. When the number of repetitions of one task performance within the three minutes reached a ceiling effect (a difference of two or less successful task completions compared to the same task earlier), the task complexity was increased according to the shaping technique (Taub et al., 1994). Tasks were divided in several categories: tasks for fine motor skills; for supination and pronation; for proximal arm movement; for sensory stimulation and sensorimotor integration. For example, one task for the fine motor skill was to pull out the pin and place in a container. For supination and pronation category, marbles were used which were in one cup and this cup was moved in pronation and supination movements to fill the marbles in an empty cup standing next to it. Another task was to turn the key clockwise and back. For proximal arm movement, one task was to place memory cards on the pedestal from the inner edge to the outer edge and vice versa. Another task was to pick up the cup and bring it to the mouth. All tasks were standardized for their positions in front of the patients and for their execution.

### 2.4 MRI acquisition

MRI was performed in a 3 Tesla whole-body MRI system (TIM-TRIO, Siemens, Erlangen, Germany) equipped with a standard head-coil.

For fMRI, contiguous multi-slice echo-planar images (TE 60 ms) were obtained in axial orientation. Thirty slices (3 mm thickness) were acquired every 2.49 s (voxel size 3 × 3 × 3 mm³).

For T1-weighted MRI, 160 sagittal slices (1 × 1 × 1 mm³ voxel size, TE 3.93 ms) were acquired.

For the probabilistic diffusion tensor imaging, a diffusion-weighted spin-echo EPI sequence was used. The whole brain was covered with contiguous 2 mm slices with an in-plane resolution of 2 × 2 mm². The diffusion encoding was performed in 61 different directions with an effective b-value of 1,000 s/mm².

### 2.5 Lesion analysis

Rorden and colleagues (Rorden, Karnath, & Bonilha, 2007) introduced the non-parametric Brunner–Munzel rank order test for the voxel-based lesion-symptom mapping (VLSM) technique to evaluate the relationship between structure (lesion) and function of human brain. They developed a software (MRIcron) with implemented tests which is freely available (www.mricron.com; Rorden & Brett, 2000; Rorden et al., 2007). A normalized T1-weighted MRI (to MRI template from the Montreal Neurological Institute) of each patient was loaded with the use of MRIcron software. In an axial formation of the T1-weighted MRI, the lesion was marked slice for slice. Thus, for each subject an intensity-defined 3D region of interest was created. Lesions were drawn by a rater who was blinded to the patients’ clinical assessments and to the fMRI results. Thereafter, a lesion overlap was calculated to create a color-coded overlay map of voxels across all patients to provide an overview of all brain regions affected by stroke.

The statistical contribution of lesion location to percent WMFT at time point post was tested using the
Brunner–Munzel rank order test for VLSM technique. In each voxel a group comparison between a binary measure (whether or not a voxel is affected by stroke) with a continuous parameter (percent WMFT at time point post) was estimated with the Brunner–Munzel rank order test resulting in a statistical map (Rorden et al., 2007). For appropriate Brunner–Munzel statistics, only voxels affected in at least 10 patient were tested (Medina, Kimberg, Chatterjee, & Coslett, 2010). To correct for multiple comparisons, all result maps were corrected using a threshold of 1% false discovery rate (FDR). For the subgroup analysis, a lesion subtraction analysis was performed. Lesions of one group were added together to create an overlap image that showed the common lesion. Lesions from the other group were then subtracted and vice versa. An image was created that showed regions that are affected in one group more than in the other group. All lesions were mapped using “MRICron.” The procedure of the lesion subtraction analysis has been described previously (Karnath, Fruhmann Berger, Kuker, & Rorden, 2004).

2.6 DTI analysis

Recovery of motor stroke is known to correlate strongly with the integrity of the CST. Therefore, DTI was used to investigate the amount of lesion to the CST. DTI data were processed and analyzed using the DTI&Fiber Tool (Department of Diagnostic Radiology, Medical Physics, Freiburg, Germany, http://www.uniklinik-freiburg.de/mr/live/arbeitssuppen/diffusion/fibertools_en.html) implemented under Matlab 2007a. First, the effective self-diffusion tensor was computed (Basser, Mattiello, & LeBihan, 1994) from the movement and distortion-corrected dataset. The diffusion tensor for each voxel of the DTI images was calculated on the realigned, non-normalized data according to Basser and colleagues (Basser et al., 1994). The unit-less fractional anisotropy (FA) is an anisotropy index and ranges from 0 in fully isotropic diffusion to 1 in fully anisotropic diffusion (Basser & Pierpaoli, 1996). According to previous reports (Stinear et al., 2007), (Fries, Danek, Scheidtman, & Hamburger, 1993), within a 5 mm radius of the posterior limb of the internal capsule, the mean FA of each patient was calculated for both the affected and unaffected side. For methodological pitfalls see Radlinska et al. (Radlinska et al., 2010). The FA-affected was evaluated as the relation of FA-Asymmetry = (FA-unaffected − FA-affected)/(FA-unaffected + FA-affected). Higher positive FA values indicate a more extended disruption of the CST. A linear regression analysis (IBM SPSS Statistics software; version 20.0) was used to determine the predictive value of FA-Asymmetry in relation to absolute values of WMFT at time point baseline and with percentage change of WMFT at time point post.

2.7 fMRI

At the beginning of the training program (defined as “baseline”) and at the end of four-week training program (defined as “post”), three active fMRI conditions were applied in a block design in two separate sessions. In both sessions, during REST, patients fixated a cross in the middle of the screen. In session one, active conditions were action observation (AO) and imitation (IMI) similar to our previous studies in healthy subjects (Hamzei, Lappchen, et al., 2012; Hamzei et al., 2016). AO is possible also in patients with severely affected hand function, while IMI was chosen to elicit maximum activation maps.

Videos of a hand grasping objects were presented with the hand from the first-person perspective. The video sequences contained hand grasping movement of the right hand in one block and of the left hand in another block. Common objects were used (like a key; an eraser). At the start of each video, patients were instructed either to only observe the video (“observe”) or to grasp the object (“grasp”). The instruction was delivered by an acoustic stimulus via headphones, controlled by a PC running “Presentation” software (Neurobehavioral Systems, Inc) synchronized to the scanner. Visual stimuli were projected onto a screen positioned in front of the bore of the scanner with a horizontal field of view of 19°. Patients viewed the visual stimuli through prism glasses.

For action observation (“observe”), only hand grasping videos corresponding to the affected hand of the patient were shown. For IMI (“grasp”), videos were shown for both the affected and unaffected hand and patients were instructed to perform the grasping movement with their own corresponding hand.

For IMI, a velcro tape was fastened around the hips before MRI acquisition and the arms of the patients were next to their body. A person in the scanner room who was not visible to the patients fixed the appropriate object to the velcro tape for each video, so that there was always one single object present. They were requested (“grasp”) to imitate the observed movement with their affected hand and in a further block with their less affected hand while watching the video. Since patients were included with severe hand function deficits, some patients were unable to perform the whole grasping movement with their affected hand according to the observed video. In these cases, patients were requested to perform the observed grasping movement as well as they could. While any change in activation maps after therapy during AO should reflect reorganization, this cannot be assumed for a task involving active movement when performance is better after therapy, because increasing complexity of a task is accompanied by an increase of functional activation (Foltsys et al., 2003; Riecker et al., 2010). Therefore, to allow distinction between activation changes induced by neuroplasticity and those induced by accelerated hand movements (Ward, Brown, Thompson, & Frackowiak, 2003), in the fMRI session after therapy (post),
Despite hand function improvement, patients were instructed to perform the same initial hand movement from the baseline fMRI. This was ensured by a protocol of the IMI performance at time point baseline. Patients performed the grasping movement and action observations five times in each block. Each REST, AO, IMI block lasted 25 s. Each active block was repeated four times and alternated in a pseudo-randomized manner with REST.

In the second session, a passive wrist movement condition (PM) was performed alternated with REST. Dorsal extensions and plantar flexions of the wrist (0°–50°) were performed once per second 25 times in a block of 25 s duration by an investigator who was not involved in training sessions and tests. This paradigm was chosen because it is independent of individual performance and possible clinical improvements and can reliably be applied to patients with severely affected hand function (Weiller, Chollet, Friston, Wise, & Frackowiak, 1992; Weiller et al., 1996).

2.8 fMRI data processing and statistical analysis

fMRI data processing was performed with SPM8 (Welcome Department of Cognitive Neurology, London, UK) running under Matlab 2007a (MathWorks). The first four images of each run were discarded to allow for equilibration of longitudinal magnetization. Calculation of online motion and distortion-corrected fMRI volumes was performed at the scanner (Zaitsev, Dold, Sakas, Henning, & Speck, 2006). Resultant volumes were spatially normalized to a symmetric template based on the Montreal Neurological Institute reference brain using the normalization parameters estimated during segmentation of the T1-anatomical scan. Since normalization in patients with large lesions might lead to incorrect normalization, we made a mask of the lesion and included it in this procedure (Brett, Leff, Rorden, & Ashburner, 2001). Normalized fMRI images were then smoothed with an isotropic 8 mm full-width half-maximum Gaussian kernel to allow valid statistical inference, according to the Gaussian random field theory (Friston, Harrison, & Penny, 2003). The images of patients with right-sided infarcts were flipped about the mid-sagittal line, such that all subjects were considered to have left-sided infarcts.

A general linear model based on a model of the time course and the hemodynamic response function was employed. Stimuli onsets were convolved with a canonical hemodynamic response function, as implemented in SPM8. Low-frequency components of fMRI time series were removed by high-pass filtering. In the second-level analyses, patients were treated as a random effect and the contrast images of the conditions of interest were entered into a two-sample t test.

We were interested in the fMRI activation change between post and baseline (post > baseline and baseline > post contrast) of AO, IMI, and PM. For a predictive activation map, we correlated the percentage change of WMFT at time point post with fMRI activation at time point baseline. We applied a threshold of significance p < .05 (corrected across the whole brain, family-wise error).

Anatomical description is based on the probabilistic cytoarchitectonic maps as implemented in the SPM Anatomy toolbox (Eickhoff et al., 2005).

Previous meta-analyses showed that stroke patients with a poor outcome recruit more contralesional and those with a good functional outcome more ipsilesional networks in motor stroke, including sensorimotor cortex (Rehme, Eickhoff, Rotschy, Fink, & Grefkes, 2012). Passive hand movement (PM) is known to lead to strong activation of the SMC and we compared for each subject the activation in SMC at post and baseline during PM (uncorrected p < .001). Subjects with an ipsilesional SMC activation were allocated to one group (group-ipsi) and those with a contralesional SMC activation to a second group (group-contra). These two subgroups were investigated further: To see whether they benefit differentially from MT, the values of WMFT-post were compared with each other. To see whether the lesion pattern differs, a lesion subtraction analysis was performed (see above lesion analysis). To see if different recovery mechanisms occur, activations for AO and IMI before and after therapy were compared in a second-level analysis (corrected FWE, p < .05).

3 RESULTS

3.1 All patients

3.1.1 Clinical outcome

Three months before starting the training program all patients showed WMFT results that were comparable with those evaluated at time point baseline. Therefore, all patients were in a stable clinical phase after stroke.

For the comparison post-training versus baseline, the results of the ANOVA indicated a significant time effect of WMFT (Greenhouse-Geisser: p < .003; \( \eta^2 \) (Eta square) = 0.207) and between-subject effects (F (1,32) = 485.907; p = .0001; \( \eta^2 \) = 0.938).

The paired t test of all patients as a group showed that in relation to baseline, WMFT continually and significantly improved (time point d7: p = .009; d14: p = .0007; d21: p = .008, and post: p = .002; Figure 1).

3.1.2 Lesion analysis

The FA-Asymmetry of the internal capsule (Stinear et al., 2007) did not show a significant correlation with WMFT at
baseline, nor with percent improvement of WMFT at time point post, thus corticospinal tract integrity did not predict the outcome of MT.

The VLSM Brunner–Munzel rank order test at time point post showed an inverse correlation of percent WMFT improvement with lesions of mainly white matter. To determine which structures of the white matter were involved, these lesions were superimposed on the results from a DTI group analysis of 30 age-matched healthy subjects (for a more detailed description of DTI analysis, please see Hamzei et al. (Hamzei et al., 2016). This overlay showed a predominant perturbation of the dorsal fasciculus longitudinalis superior (SLF) and the ventral stream passing through the extreme capsule (EmC; Figure 2). With SLF we denote here the conglomerate of SLF II and III (and probably AF), the VOI in the extreme capsule contains the ventral fronto-temporal fibers, contributing to what is called the EmC tract, including the Uncinate fascicle as well.

### 3.1.3 | fMRI

During “action observation” (AO) of the affected hand, activation of both dorsal premotor cortices (dPMC; x-, y-, and z-coordinates: 42, 12, 39 and −42, 15, 36) decreased after MT compared with baseline (Figure 3).

“Movement imitation” (IMI) of the affected hand after the MT program showed an activation increase in the ipsilesional supplementary motor area (SMA; x-, y-, and z-coordinates: −9, 15, 66) and in the ipsilesional cerebellum (with two maximum peak voxels: x-, y-, and z-coordinates 0, −66, −27 and 9, −66, −27) compared with baseline. IMI of the unaffected hand showed a decreased activation in the contralesional SMA after MT (x-, y-, and z-coordinates: 0, 6, 54), caudal to SMA activation of IMI of the affected hand, as well as a decreased activation in the contralesional pallidum (15, 0, 3).

The fMRI activation during passive wrist movement (PM) did not show any difference in the contrast post versus baseline and vice versa for the entire group.

The correlation of fMRI activation for PM, IMI, and AO at baseline with post-WMFT in the whole of patients did not exceed the level of significance, so fMRI at baseline did not predict the outcome of MT.

### 3.2 | Subgroups

In a single-subject analysis of PM activation of the affected hand two groups could be differentiated: fMRI showed a stronger ipsilesional than contralesional activation in sensorimotor cortex in 17 patients after MT, these were assigned to group-ipsi. The other 16 patients showed a stronger contralesional than ipsilesional activation in SMC, these patients were assigned to group-contra. In the direct comparison between both groups, the activation
in ipsilesional SMC of the group-ipsi was significantly stronger compared to group-contra, and the activation in contralesional SMC was significantly stronger in group-contra compared to group-ipsi. The same analysis as for the whole group of patients was performed in these two subgroups, for clinical outcome, activation patterns and lesion description (Figure 4).

### 3.2.1 Clinical outcome

Patients with ipsilesional SMC activation during passive wrist movement of the affected hand fared markedly better. Patients in group-ipsi showed a stronger increase of 168% in WMFT whereas group-contra only had an increase of 6% (level of significance of the between group analysis for day 7: \( p < .01 \); day 14: \( p < .003 \); day 21: \( p < .016 \); and post: \( p < .004 \)).

### 3.2.2 Lesion analysis

The FA-Asymmetry in the internal capsule did not differ between the two subgroups.

The lesion subtraction analysis of both groups demonstrated that group-ipsi did not reveal more extended lesions than group-contra (no difference in volume size), while group-contra showed more extended lesions in the white matter in comparison with group-ipsi. Superimposing this lesion subtraction analysis map again onto a map detailing the dorsal fasciculus longitudinalis superior (SLF) and the ventral EmC (see A2 above) demonstrated that the more extended...
3.2.3 | fMRI

The two subgroups were defined by their PM activation of the affected hand after MT, but at baseline there was no significant difference of activation during PM between the groups, consequently also in the subgroups, PM at baseline did not predict recovery.

For IMI, there were no differences between the subgroups for the affected and for the unaffected hand, neither before nor after MT.

For AO, before MT there was no significant difference between the two subgroups in a direct comparison. After MT, the group-ipsi showed significantly stronger activation in left (ipsilesional) frontal areas than group-contra, in ventral premotor cortex, the inferior frontal gyrus (IFG) including BA 44 and BA 45, and BA 46. In contrast, the group-contra showed stronger activation than the group-ipsi in the left inferior parietal lobule (IPL).

For IMI, there were no differences between the subgroups for the affected and for the unaffected hand, neither before nor after MT.

4 | DISCUSSION

4.1 | All patients

In accordance to previous studies, mirror therapy (MT) improved function in our chronic stroke patients. The score of WMFMT for the affected, untrained hand increased from baseline for each week during the four-week period of training. At
the end of training, the average score was about 138% of baseline. This should translate to a noticeable difference for patients in functional tasks with the affected hand, since WMFT was developed to reflect performance in daily life activities.

Many studies have shown that recovery after motor stroke depends on the integrity of the CST (Stinear et al., 2007). For example, in one previous study with forced-use therapy for motor stroke, 6 months follow-up showed that clinical improvement was only transient in patients with lesion of the CST (Rijntjes, Hamzei, Glauche, Saur, & Weiller, 2011). In the present study, however, we did not find any relationship between the FA-Asymmetry of the affected CST and change...
of WMFT after 4 weeks. This discrepancy might be due to the essentially different networks targeted by different therapies. Whereas forced-use therapy is based on continuous stimulation of the lesioned hemisphere (HS) via training of the affected arm, especially the ipsilesional primary motor cortex and the CST emanating from this area, MT tries to gain access to networks in the affected HS indirectly through secondary areas in the unaffected HS (by training of the unaffected arm in the mirror). For MT, the effect is not determined by CST integrity, it was the long association tracts which played the decisive role here. WMFT changes inversely correlated with the integrity of SLF and EmC tracts. Thus, lesioning of one or both these two long association tracts is the determinant factor for the capacity of recovery with MT.

The only areas that showed an activation change after MT in the whole group were in the dorso-dorsal stream, that is, bilateral dPMC and SMA. During AO, similar to the previous study in healthy volunteers, MT let to a decrease of activation of dPMC in the HS contralateral to the untrained hand and it was assumed that transcallosal connections between areas of the visual dorsal stream play a major role in the illusion during MT that the resting hand is performing tasks. In the present study, AO of the untrained affected hand after MT showed not only a decrease in the contralateral dPMC but also in the ipsilateral dPMC, which did not reach significance in healthy volunteers after MT (Hamzei, Lappchen, et al., 2012). This underlines the importance of the transcallosal connections of dPMC for MT. Bilateral dPMC showed a decrease of activation, and a decrease of activation after a learning process is generally interpreted as reflecting successful reorganization (Hamzei, Glauche, Schwarzwald, & May, 2012; Ward et al., 2003), demanding less energetic expenditure. Also similar to the previous study, after MT the SMA contralateral to the trained hand showed a decrease in activation during IMI. It was hypothesized that also the SMA plays a role in the illusion conveyed by the mirror, because of its involvement in bimanual coordination tasks.

In the previous study in healthy volunteers (Hamzei, Lappchen, et al., 2012), IMI was associated with an increase in activation in SMC in the HS contralateral to the untrained hand when compared with volunteers who trained without a mirror. In the present study, we did not observe this activation increase in SMC during IMI in the ipsilesional, untrained HS, most probably due to the restriction we put upon the patients to perform the grasping tasks before and after therapy with the same performance. However, after MT there was still an increase in the associated ipsilesional SMA during IMI. According to the roles ascribed to the SMA, this might either reflect an increased internal processing of the task that was learned by the illusion that was performed with the affected hand, or that the volition for the generation of the cued movement has become stronger after therapy.

In sum, activation changes during AO and IMI in the dorso-dorsal stream confirm the interhemispheric and bimanual interactions in areas also found in healthy subjects, but they fail far short of explaining why MT improves performance. We could not establish a correlation between amount of activation changes and amount of WMFT improvement. We did not find any involvement of the ventro-dorsal stream (vPMC and IPL) neither in the unaffected HS contralateral to the trained hand (like in the previous study in healthy volunteers), nor in the affected HS, which would have indicated that the training has led to storage of learned movement parameters (Michielsen et al., 2011; Rehme et al., 2012).

Also, there was no indication that the MNS, based on the ventro-dorsal stream, might have interacted with the ventral stream. Observation is closely connected to understanding the observed action as shown in a previous study, where the MNS and the ventral stream interacted in the IFG (Hamzei et al., 2016). Although in that previous study involvement of the ventral stream became significant only in a larger group of subjects than the present patient group, we expected that for patients, the higher effort to process the illusionary movement in the affected HS would have led to activation changes in areas belonging to the ventral stream.

The fact that WMFT improvement was inversely correlated with the amount of lesion to the ventro-dorsal and ventral EMC tracts does point to a role of the ventro-dorsal and ventral stream in recovery when using MT, but leaves open the answer to the question which mechanisms patients do use to improve performance. Above all, since ultimately any therapy for motor stroke is expected to exert influence on the main output area, the SMC, passive wrist movement did not show a difference in activation in this area before or after therapy, nor did it correlate with the amount of WMFT improvement. However, these findings in the whole group of patients contrary to expectations and insufficient for explaining the mechanisms behind recovery after MT are resolved when investigating the results in the subgroups.

### 4.2 Subgroups

When dividing the patients according to their activation pattern in predominantly ipsi- or contralesional SMC after MT as evoked by PM, a clear differentiation in clinical outcome, lesion location and activation pattern becomes apparent. Patients with ipsilesional SMC activation after MT had a larger improvement in WMFT (168%) than patients with contralesional SMC activation (only 6% improvement). Apparently, improvement in the whole group of patients was driven by the group-ipsi. In other words, patients in whom
MT is able to evoke ipsilesional motor cortex activation fare better.

Again, the FA-asymmetry did not differ between the two groups, so the capacity for improvement did not depend on the amount of lesion to the CST. However, the lesion comparison between the two groups shows that lesions in the group-contra were larger than in the group-ipsi and affected both the SLF as part of the ventro-dorsal stream and the EmC tract as part of the ventral stream.

This explains why in the whole group, no relation between WMFT improvement and involvement of the ventro-dorsal and ventral streams of the dual loop model was found. Only when these tracts are intact, a successful reorganization can take place, and the mechanisms behind this are revealed when observing the difference in activation pattern during AO of the affected hand after MT.

In group-ipsi, AO after successful therapy is associated with an increased activation in the affected hemisphere in frontal areas that constitute the projections of both the ventro-dorsal stream and the ventral stream. For the ventro-dorsal stream they include vPMC and BA 44. Also, BA 46 as part of the dorsolateral prefrontal cortex is activated more strongly and this area is functionally associated with attention and working memory, so that it might be regarded as part of the ventro-dorsal system. For the ventral stream it includes BA 45, demonstrating that MT is successful when the affected HS is able to perform a sequence- and time-independent structural analysis of the illusionary movement. These frontal areas in the IFG were the same ones that were found in a previous study on AO where the MNS and the ventral stream for structural analysis interacted (Hamzei et al., 2016). Thus, both projections of the ventro-dorsal and ventral streams were activated in successful MT, suggesting that the interaction of both streams is a prerequisite for successful reorganization in MT. In contrast, group-contra did not show any involvement of the ventral stream. Only the postrolandic part of the ventro-dorsal stream (the IPL in the affected HS) was activated more strongly during AO after MT than before therapy. Since the anatomical connection with the frontal areas was severed, no further sequential analysis or consolidation was possible in these patients, and they did not improve after MT.

Like in the whole group, IMI did not show a difference in activation before or after therapy in the group-ipsi and group-contra. But again, this is most probably due to the fact that we instructed the patients to perform the task after therapy in the same manner as before therapy.

There are some limitations to this study. We did not investigate a control group. However, the current study investigated chronic stroke patients with a stroke at least 1 year before and with a stable clinical level over the last 3 months before the start of MT. The rehabilitation period was limited to 4 weeks, and for any rehabilitation therapy based on knowledge of anatomical and functional deficits, longer follow-up will be necessary to see whether patients will maintain their improvements over time. It is very well conceivable that those patients who did not benefit from MT would have benefited from another rehabilitation approach. This warrants further investigation, but in any such study we suggest that the anatomical lesion location and the capacity for activation of the remaining network by another specific therapy will have to be considered.

5 SUMMARY

Taken the results from the whole group and subgroups together, the following picture emerges:

The access to areas in the affected HS during MT when training the unaffected hand is obtained via the dorso-dorsal stream, especially through bilateral dPMC. However, to induce meaningful reorganization, both the ventro-dorsal and ventral stream of the affected HS have to be involved. The result is a stronger activation in the ipsilesional SMC, contralateral to the affected hand, correlating with a stronger clinical improvement. Therefore, the present data show that only in patients in which ventro-dorsal and ventral tract fibers of the dual loop model are not affected and an interaction between these two streams in IFG is possible, MT can induce clinical improvement.

It is interesting to note that information from all three parameters: clinical improvement, lesion analysis, and activation patterns, was necessary to understand which patients benefit from MT. Clinical improvement alone was not enough, since a subgroup of patients with lesions on the ventro-dorsal and ventral streams did not profit from MT. Identification of these patients, however, was only possible after looking at the activation changes in SMC. The activation patterns in the subgroups during AO revealed the mechanisms behind successful reorganization. We suggest that in the future, studies that want to determine the beneficial therapy for a certain group of patients need to consider all three parameters. In our opinion, the present study strongly suggests that this is a necessary step to achieve the goal of individualized therapy for single patients.

CONFLICT OF INTEREST

All authors disclose any potential sources of conflict of interest.

AUTHOR CONTRIBUTIONS

FH designed the study, completed the study protocol, carried out the MRI investigations and analyzed MRI data, analyzed the tests, interpreted the results, and wrote the manuscript. GE and UK carried out the therapy and testing of patients. CW gave advice to the study design, interpreted
the results, and wrote the manuscript. MR gave advice to the study design, interpreted the results, and wrote the manuscript.

**DATA ACCESSIBILITY**
We will provide our data from current study. If there is any interest please contact farsin.hamzei@moritz-klinik.de

**ORCID**
Farsin Hamzei [https://orcid.org/0000-0003-0036-4368](https://orcid.org/0000-0003-0036-4368)

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