PERSISTENCE OR PLASTICITY: EXAMINING HAND REPRESENTATIONS SUBSEQUENT TO CORTICOSPINAL TRACT LESIONS USING FMRI

by

Anna Schwarz

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Anna Schwarz

Approved: _____

Jared Medina, PhD
Professor in charge of thesis on behalf of the Advisory Committee

Approved: _____

James Hoffman, PhD
Committee member from the Department of Psychological and Brain Sciences

Approved: _____

Anna Klintsova, PhD
Committee member from the Board of Senior Thesis Readers

Approved: _____

Michael Chajes, Ph.D.
Chair of the University Committee on Student and Faculty Honors

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ABSTRACT

It has been widely accepted that plastic changes occur after damage to the brain to aid in functional and structural recovery. While there is ample evidence that plastic changes do indeed occur after damage, there is also evidence that certain representations within the brain may be preserved and unaffected by plasticity. Neural correlates of phantom limbs have been studied in depth, but no literature exists on the representations of paralyzed limbs in stroke patients after subcortical stroke resulting in hemiparesis. We utilized Representational Similarity Analysis to compare hand representations in primary motor (M1) and sensorimotor (S1) cortices of subcortical stroke patients to address the extent to which paralyzed hands representations are maintained after years of paralysis. Two patients (n = 2) with lesions to the corticospinal tract and intact motor cortices underwent functional MRI runs in which they were asked to perform individual digit movements on both hands. Functional activity for intact and paralyzed limb movements were then analyzed using RSA to map out hand representations in terms of inter-digit relationships. Paralyzed hand representations in both contralateral M1 and S1were found to be organized in a manner consistent with those of normally working hands. The ability to decode the digit relationships of a hand during "movements" of paralyzed limbs demonstrates that hand representations are preserved in M1 and S1 even after years of paralysis. This facilitates an investigation into the role of peripheral signals in maintaining the function and structure of bodily representations after brain damage.

Chapter 1

INTRODUCTION

Neuroplasticity

Broadly, the term neuroplasticity refers to the brain's natural ability to adapt to change through changing its structure and function (Nudo 2009, Kolb 1998). Plasticity allows us to learn new information and skills throughout our lifetime, such as increasing gray matter volume in areas specific to London taxi drivers who have to retain detailed spatial maps, as shown in Maguire et al., 2000. Often times spontaneously, the brain will initiate specific mechanisms that are meant to aid in its own recovery. Whether that may be forming new synaptic connections or reorganizing previously established ones, the brain is able to restructure itself as a way to deal with the damage that has been done to it (Carmichael, 2003). Patient populations have often been studied for their brain changes after damage to see how, specifically, the brain adapts to a distinct change in its own function. After damage to the brain or to body parts that send signals to and from it, the brain's functionality is changed to compensate for the injury, which may involve rewiring of functional networks (Wall 2002). Not only do functional networks adapt, but the actual structure of the brain can as well. Langer et al., 2012 showed that increased immobilization (reduced sensory input and motor output of a limb) led to a decrease in cortical thickness of the portion of the brain representing that limb, which further illustrates how the brain is able to respond to peripheral changes. Interestingly, the sensory experience of having a

phantom limb in amputee patients as opposed to lack of that sensory experience in congenital one-handers may mediate the lasting representation of the missing limb (Wesselink et al 2019). While there is ample evidence for plastic changes occurring after damage to the brain, this study in specific poses questions on the extent to which (if at all) these changes occur after damage.

Stroke has been widely shown to induce plastic changes (Gauthier et al., 2008), most of which are variable depending on location and nature of lesion. The brain may unmask underlying connections that weren't previously in use, or structurally reorganize the pathways that were in use to attempt to recover from the damage that has taken place. The somatotopic layout of the brain is organized in a manner such that different body parts are represented in different areas of cortex adjacent to and overlapping with one another, so that our brains can effectively send and receive signals to and from the correct body part. In adult monkeys, somatosensory maps have been shown to reorganize such that the neighboring face area extended into the affected hand (Pons et al., 1991). Similarly, in upper limb amputee patients, the face region has also shown to extend into the cortex of the amputated hand area (Maclver, 2008 and Flor et al. 2006). This shifting of the face region into the hand area has been thought to play a role in sensations of phantom limb pain in amputee patients. Given that these changes have been associated with phantom limb pain, the concept of reorganization of somatosensory cortex after peripheral changes has been caused the **maladaptive plasticity hypothesis** (Flor 2008).

On the other hand, the **preserved structure function hypothesis** states that the cortex previously representing the affected limb still represents it, even without peripheral signals. Makin and colleagues (2013) challenged the maladaptive plasticity

hypothesis, showing that phantom pain is associated with preserved structure and functional organization of the missing hand area. More recent studies with amputees have shown that hand representation persists even long after amputation (Kikkert 2016), proposing that the cortex lacking peripheral input (for the amputated hand) is not completely repurposed. This study is pertinent to my thesis project and will be revisited later in more detail. Furthermore, within the visual cortex following macular degeneration, the functional representation of the intact visual field was absent, suggesting a lack of functional remapping after brain damage (Baseler et al., 2011). The variability in these results from different studies on specific plastic changes after brain damage brings questions about the specific changes that may or may not occur after certain injuries.

Motor Plasticity

Motor deficits after stroke, particularly in the upper extremities, are common, with recovery outcomes being quite variable. Fine movement of contralateral limbs is mediated by the corticospinal tract (CST), which carries signals from the primary motor cortex, M1, to the body to initiate movement. Both animal models and humans have provided evidence for post-stroke neuroplasticity in regard to motor recovery. Starkey et al., 2012 found that in rats with lesions in M1 forelimb region, corticospinal projections from the hindlimb region reinnervated the upper limb region. Additionally, in humans with motor impairments after stroke, compensatory movements of different body parts due to the absence of movements from affected limbs cause shifts in somatotopic maps (Cirstea and Levin 2000). In studies using Transcranial Magnetic

Stimulation (TMS) after stroke, the excitability of the affected motor cortex is reduced as well as the cortical representation of the affected muscles (Traversa et al. 1997).

The corticospinal tract is important in studying functional recovery and plasticity after stroke during motor deficits as it is the major pathway that carries motor signals from the brain to the rest of the body to initiate motor movements. Rosso and colleagues (2013) showed that upper limb motor function following stroke was determined mainly by the integrity of the CST. While motor activity ventral to the ipsilesional motor cortex of paretic hands in stroke patients has been shown during paretic hand movements (Schaechter et al., 2008), the nature of this activity has not been thoroughly investigated. Schaechter and colleagues (2008) relate the extent of structural damage to the CST with functional reorganization, while the current study proposes a lack of functional reorganization with CST damage. TMS on the affected hemisphere of stroke patients that produced no motor-evoked potential (MEP) has also shown to predict low functional potential for recovery (Stinear et al. 2007).

While the results from these studies seem to outline the case that there is a point of no return at which the ipsilesional cortex does not generate signal for the affected limb, this may not be the case. It could be that, given the nature of the lesion, the motor cortex is completely intact and able to generate a signal, but the pathway that is sending the signal from M1 to the CST is severed, causing the body to be unable to move in response to the TMS pulse. In the current study, we address this possibility by using patients with intact motor cortices and subcortical lesions to the CST to analyze the activity in their ipsilesional M1 during “movements” of their affected limbs. This way, we can examine whether the undamaged motor cortex is able to generate a signal that is not “received” by the limb due to the damaged CST.

Any activation during these attempted movements "movements" of the damaged limb would then indicate a signal generated by a movement that is not taking place, possibly due to a lasting representation of the damaged limb.

So, given that the patients whom we are studying have intact motor cortices, there are two possibilities for the functional data during affected limb movements. One possibility is that sending a motor command no longer produces a signal in the motor cortex, perhaps due to post-stroke plastic changes that took place due to a loss of peripheral input to the area dedicated for the affected limb. It could be that new or unused pathways have now taken over the region previously responsible for hand movements. Alternatively, we could see maintained activation in the ipsilesional motor cortex during attempted movements of the paralyzed limb. This would provide evidence for the hand still being represented in some way in M1 of the affected hemisphere, even years after paralysis. This would indicate that, even with a large timeframe for plastic changes to take place, the changes did *not* occur.

In a previous study completed in the Medina lab with the same patients, motor activity during paralyzed limb "movements" was shown in the ipsilesional motor cortex (details of which are explained more in the Results section.) Given this activity, we aimed to find out whether the activation displayed the representational nature of a hand. The activation pattern could be completely random, or, it could be that it reflects the activity pattern of a typical intact hand. If the neural activation pattern does represent a typical hand, then we will be able to see specific patterns for each individual digit, and specific relationships between the activations of the digits that is statistically similar to that of the intact hemisphere, given that we did not use control participants.

Representational Similarity Analysis

Representational Similarity Analysis (RSA) has been used recently to analyze the similarity between representations of functional activity patterns in specific regions of the brain. Kriegeskorte et al. 2008 proposed the methodology through the use of representational dissimilarity matrices. The dissimilarity matrices are computed by comparing activity patterns for individual experimental conditions, and then comparing the dissimilarity between each pair of conditions by calculating an index of distances between them. Values closer to 0 are closer in value, thus, more similar, and values further from 0 are further in value, and more dissimilar.

RSA has been used to examine the extent of lasting representation of limbs in amputee patients as it relates to phantom limb sensations. Recent studies have used RSA to show that representation of amputated hands remain in the primary somatosensory cortex decades after amputation (Kikkert, et al., 2016). In these studies, the experimenters asked amputees and controls to make individual finger movements with their real or phantom hands. In doing so, the representation pattern of controls can be used to model the representation pattern for an intact, normally functioning hand. This model of a hand representation can then be used to compare representation patterns seen in amputee's phantom limbs to examine the similarity between the representations. Thus, similarity in these patterns are indicative of a continued representation of amputee's missing hands. In a follow up study using congenital one handers along with amputee patients, RSA was used to compare how similar the representations of missing hands are in the different populations with similar deficits (Wesselink et al., 2019). This study revealed the importance of the sensory experience to the lasting representation previously seen in the somatosensory area, as congenital

one handers did not have vivid phantom sensations, and their hand representations showed virtually no difference between digit movements. Furthermore, individual finger movements have shown to have consistent relationships with one another in terms of functional activity patterns (Ejaz et al. 2015). Our hands are represented in our brains in a specific organization that allows us to use them in a controllable and functional way during everyday life. This representation can be used as a baseline for comparisons with representations of damaged or missing limbs. Specifically, by finding activation patterns of each individual finger movements, as Kikkert et al. 2016 and Wesselink et al. 2019 did, we can observe the difference between these activation patterns and the relationships *between* each digit. This set of differences can be used to define the "normal" hand representation in terms of comparisons between each digits. Together, these papers provide evidence for using RSA as a way to decode the precise nature of certain functional patterns of activity in the brain, specifically hand movements. Additionally, they provide evidence against the idea that the cortex missing peripheral signals becomes repurposed, and support the preserved-structure function hypothesis surrounding plasticity, possibly due to the overwhelming importance of the hand prior to damage.

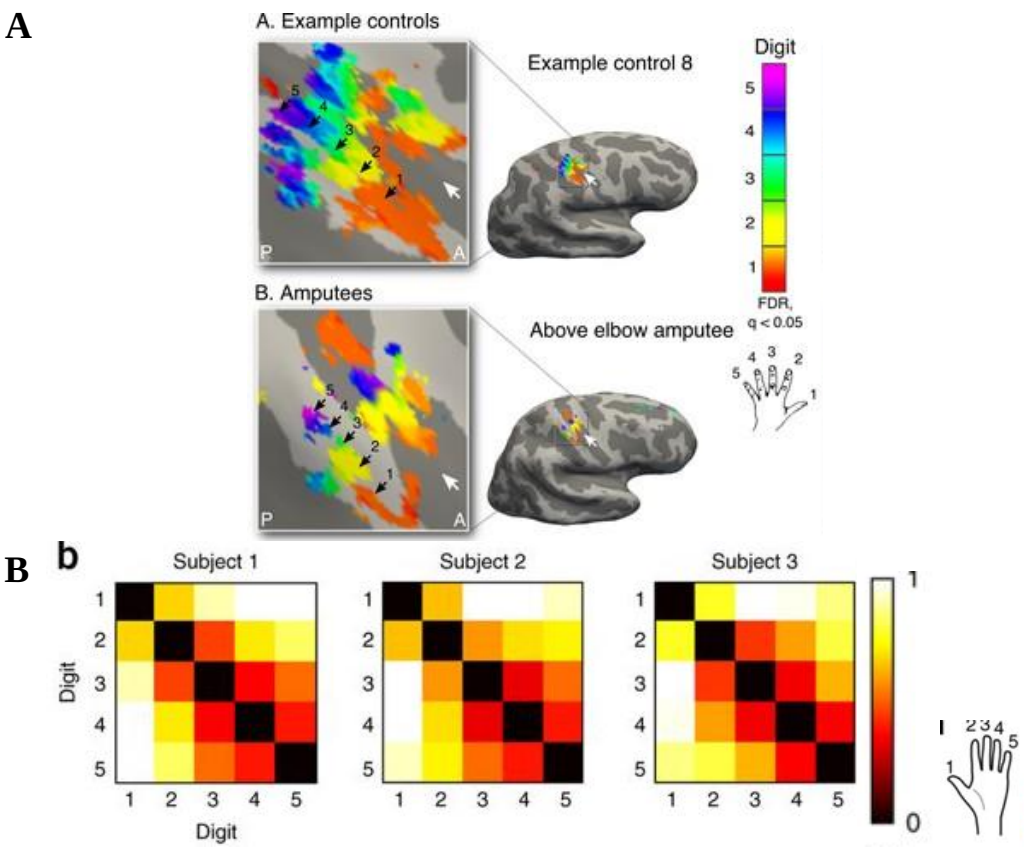


Figure 1 1A: Figure taken (and cropped) from Kikkert et al. 2016 showing neural activation patterns for amputee's phantom limbs and control subject's intact limbs during movements of individual digits, and the similarities between them. 1B: Figure taken from Ejaz et al. 2015 showing representations for hands of healthy subjects in M1 during individual digit movements. Distance values represent Mahalanobis distances, values closer to 0 show 0 dissimilarity while values closer to 1 show higher dissimilarity.

Current Project

We know that amputee patient's phantom limbs have representations that are preserved even decades after amputation (Kikkert et al., 2016). This finding raises questions on the importance of peripheral signals in maintaining a representation in the brain for the affected limb. However, the question of lasting representations of paralyzed limbs in stroke patients has not been addressed. While there has been ample evidence to suggest rapid onset of plastic changes after stroke, there has been little investigation into whether or not there are specific constraints on this plasticity that may prevent it from occurring. The current study aims to provide data on how stroke patients represent their paralyzed limbs in their affected motor cortex years after paralysis, and whether or not the representation is consistent with that of their intact hand. The patients that we tested all have intact ipsilesional M1 and subcortical lesions to the CST, meaning that there is no pathway for the motor signal to be sent to the affected hand, resulting in paralysis. We know that these patients have ipsilesional M1activation during "movements" of their paralyzed limb (as found in a previous study done in the lab, detailed in the Results section), so we want to analyze the particular nature of these activations. In particular, we want to investigate whether or not the paralyzed hand movements display a distinct organizational pattern that is representative of a normal functioning hand. The use of RSA allows us to compare the functional activity patterns of individual digit movements to the activity patterns of the other digits in order to model these relationships in terms of how the hand is represented in the brain. With this, we are able to estimate a representational structure of the hand for patient's intact and affected hands, which allows us to analyze the extent to which the representation patterns between hemispheres differ.

In this thesis, we address three principal questions: 1) years after stroke, do patients still represent their hand in M1 of the damaged hemisphere, 2) is this representation different from the representation in the intact hemisphere and 3) are there other brain regions that represent hand movement as seen by using RSA. We expect to see similar representations of the hand in the intact and affected hemispheres of the patients through similar inter-digit relationships. If, years after stroke, we see that the organizational representations are similar, then this is evidence that the hand representation of the paralyzed limb is not necessarily influenced by peripheral input to the brain, as the patient's limbs have been paralyzed for multiple years. This research will provide data on the extent to which plastic changes affect hand representations in paralyzed stroke patients affected limbs, which will open up new questions on the specific mechanisms that take place to either retain or diminish these representations. This data could potentially lead to new technology that will be able to incorporate the specified hand representations, composed of distinct neural patterns for each digit, in a way to improve neurorehabilitation after stroke, possibly by finding a way to bypass the lesion and carrying the signal to the CST to execute movements in the affected limb. Additionally, the data will allow for the possibility of direct and indirect comparisons to other patient populations under similar circumstances, such as amputee patients, to see how similarly limbs that are no longer in use are represented after two different traumatic events to the brain.

Chapter 2

METHODS AND MATERIALS

Participants

The stroke patient database from previous research projects in the Cognitive Neuropsychology Lab of Dr. Jared Medina at the University of Delaware was used to find participants for the current study. Eligibility included 1) lesions that did not extend into the motor cortex in the ipsilesional hemisphere (checked using FSL) and 2) scores of zero on tactile localization and grip strength assessments (to be described in the next section). For all of the patients that fit the preliminary criteria, DTI fiber tracking was completed using FSL to reconstruct the corticospinal tract. There were 6 patients who fit these criteria, all of whom were invited back to University of Delaware to participate in this study. Of those invited, four came back to participate, but only two patients' data were able to be used. One patient requested to leave the scanner before testing was completed, and another patient had excessive head movement during some of his functional runs**.**

Patient Age	**Lesion Location**	**Lesion Date**	**Grip Strength Score**	**Tactile Localization Score**
83	Left claustrum, external and internal capsules	07/14/2010	0	0

72	Right claustrum, external and internal capsules	10/28/2005	0	0

Table 1 Patient information for the two individuals whose data was used for the study.

Behavioral Data

First, we wanted to test basic motor performance, to examine if their hand was paralyzed. This was done to ensure that, if there was activity found in the motor cortex of the paralyzed limb, it would not be due to a motor signal reaching the limb.

Two main tasks were used to address the motor ability of the patients, grip strength and finger tapping. During the grip strength task, patients were asked to squeeze a device, 3 times on each hand, that then output a number corresponding to the received strength of their grasp. During the finger tapping task, patients were asked to tap their index fingers on both hands, 5 times for each hand, for 30 seconds, and the total number of taps was counted. For this thesis, we selected participants who scored a zero on both tasks.

MRI Tasks

Participants completed a single experimental session of four fMRI runs with a block design. The task involved 6 conditions; individual movements of each of the 5 fingers and a rest condition. A run was repeated twice on each hand in a

counterbalanced Left – Right – Right – Left order which was switched with Right – Left – Left – Right every other participant.

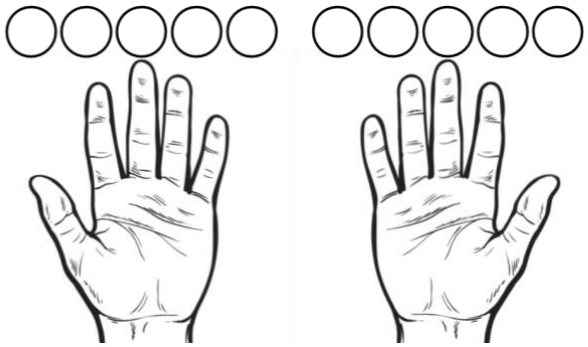


Figure 2 Stimuli shown to the patients in the scanner above corresponding fingers that the patients moved when the circle flashed red.

As shown in Figure 2, the participant was first presented with 5 blank circles, corresponding to the five digits, in a straight horizontal line shown on a visual display projected into the scanner bore. A red flashing circle indicated which digit the patient was instructed to move (in a flexion / extension manner) for the duration of the time that the circle remained flashing. The patient's hands were oriented palm face up, so that for left hand blocks, the leftmost circle indicated that the subject should move the thumb, and on right hand blocks, the pinky. Each trial lasted 12 seconds and was repeated 7 times throughout one block, resulting in one block lasting 8 minutes and 24 seconds. One full run (consisting of 4 blocks) in the scanner lasted 33 minutes, plus the structural scan at the beginning lasting 6 minutes resulted in a total scan time of 39 minutes. The patients were instructed to try as best as they can to perform actual movements with their paralyzed hands as opposed to just imagining the movement,

even though it was understood that no movement would actually occur. This was emphasized to the patients before scanning, and we explained to them the importance of trying to actually move their paralyzed limb. To make sure that the patients understood these instructions, there was a practice round before they went in to the scanner using their intact hand.

On occasion, mirror movements have occurred in stroke patients during movements of their paretic limbs (Nelles 1998). Mirror movements are movements of the ipsilesional limb when attempting to move the contralesional limb. Furthermore, we wanted to ensure that there was no activity in the paralyzed limb. To examine both of these, two MRI compatible Electromyography (EMG) electrodes were attached to each arm. The EMG electrodes were placed halfway between the elbow crease and wrist at a location where the muscles could be felt moving when participants were asked to do so. Additionally, a ground electrode was placed on the participants ankle. The EMG data has been collected and pre-processed, however, due to time constraints, the data has not yet been analyzed.

MRI Acquisition

Patients were scanned in a 3T Siemens MRI scanner with a 64-channel head coil. Structural scans were acquired for all patients using the following acquisition parameters: TR = 2080 ms, TE = 4.64 ms, flip angle = 9 degrees, voxel resolution =.7x.7x.7 and voxel slice thickness .70 mm. Functional images were collected using a singleband T1 weighted pulse sequence with the following acquisition parameters: TR = 1000 ms, TE = 32 ms, flip angle 61 degrees, slice thickness 2.0 mm, and voxel resolution 2x2x2. The total number of volumes collected per functional run = 516.

FMRIB Software Library (FSL) was used to pre-process and analyze the images. The following steps were included: Motion correction using MCFLIRT (Jenkinson et al., 2002), brain extraction using BET brain extraction tool (Smith, 2002), spatial smoothing using a 2mm FWHM (full width at half maximum) kernel, and high pass temporal filtering with a cut-off of 100s. Co-registration to each individual anatomical T1 scan was accomplished using FLIRT.

DTI Analysis

Diffusion-weighted images were acquired using the following acquisition parameters: TE = 106.0 ms, TR = 5300 ms, voxel resolution = 1.4 × 1.4 × 4 mm, 35 sagittal slices, 64 diffusion-directions with a diffusion weighting of b = 1000 and b = 0. A T1-weighted structural image was acquired using an MPRAGE sequence with parameters: TR = 2080.0 ms, TE = 4.64 ms, flip angle = 7°, voxel size = 0.7 × 0.7 × 0.7 mm, 208 sagittal slices.

Images were processed and analyzed using the FSL package (FMRIB Software Library v5.0, Oxford, UK). For preprocessing, the diffusion-weighted image was first corrected for eddy currents and susceptibility. Next, the 3D image with no diffusion weighting (b=0) was brain-extracted using the BET tool, and then co-registered to the T1-weighted structural image.

Tractography analyses were performed using the FDT diffusion toolbox in FSL. First, diffusion parameters were estimated using the BEDPOSTX tool. To reconstruct the CST, ProbtrackX was run using an estimation of fibers from M1 to the lower pons level of the ipsilateral side with the following parameters: number of samples = 5000, curvature threshold =.2. Circular seed masks of radius 5 mm were

made on the primary motor cortex in both hemispheres, along with 2.5 mm terminal masks on the lower pons level on both sides of the brain. Exclusion masks were made for the cerebellum and between hemispheres to avoid projections outside of the ipsilateral M1 to CST route. The threshold for the fibers that were looked at was 1/10 of the total that appeared in FSLview of the outputted fiber tract data from each ProbtrackX run. Reconstructed fiber paths of the CST are shown in the figure below, which show a clear cut off point in the damaged hemisphere where the signal terminates on its way out of the brain and to the body. For the damaged hemisphere, the lowest FA value was 0, and for the intact hemisphere, the lowest average FA value was found to be .33 and .27 for Patient 1 and Patient 2, respectively.

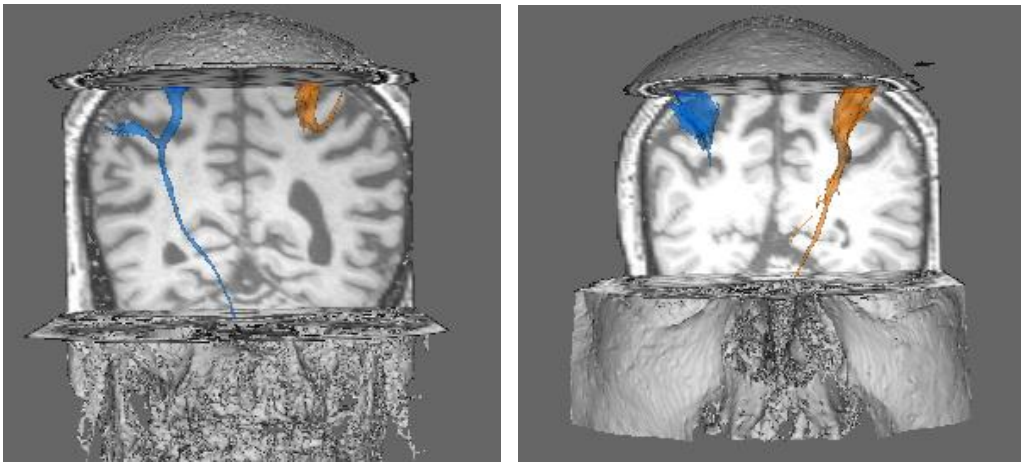


Figure 3 Fiber paths of the CST constructed with DTI data for the two patients tested. Patient 1 (on the left) had paralysis in their right hand, while Patient 2 (on the right) had paralysis in their left hand.

Fractional Anisotropy (FA) values were calculated for each fiber path created using whole brain FA value maps outputted by DTIFIT. First, the 3D image with no

diffusion weighting (b=0) was registered to the T1 image for each patient. Next, whole brain FA maps (output during the DTIFIT step) were co-registered in the patient's individual T1 space. The fiber path maps that were outputted from the ProbtrackX probabilistic tracking were then binarized and thresholded to 1/10 of the total fibers. Individual masks of 6 mm were made every 20 voxels in the y direction along this thresholded and binarized FA value map.

MRI Analysis

Standard Event Related Analyses

First-level analyses of functional runs were done using FSL's FEAT function with a high pass filter cutoff of 100 using a Voxel Wise General Linear Model (GLM). Regressors were created modeling the stimulus presentation timing (corresponding to individual finger movements) to a Double-Gamma hemodynamic response function (HRF) deconvolution wave form. We computed a single contrast for each finger movement against rest periods, resulting in 5 distinct activation patterns for each finger. At the end, we computed an F test which collapsed the activity of each finger against rest to have a localizer of the hand area in both hemispheres.

Inter-digit Representational Similarity Analysis

Since the main objective of our experiment is to show the motor representation of the paralyzed hand, our main analysis was restricted to hand selective M1. Given that both participants showed M1 activation both during intact and paralyzed hand movements, we drew the masks using functional data obtained from the F test in the

first level analysis. Sun et al. 2015 showed that finger movements elicit activation of the primary somatosensory cortex, S1, so additional functional masks were drawn on S1 to see if hand representations exist here as well. Masks were drawn in both hemispheres using functional and anatomical landmarks to identify the ROI.

The activity patterns used for RSA correspond to the voxel-wise parameter estimation for each individual finger movement and the residuals of the models within each ROI. The dissimilarity between each digit pair was measured by computing the cross-validated Mahalanobis distance (Nili et al., 2014), using a Matlab toolbox adapted for FSL output data. Daan Wesselink, PhD student at University of Oxford, kindly sent this toolbox to our lab upon request. We used cross validated Mahalanobis distance because it is more resistant to multivariate noise (Diedrichsen et al. 2016). Before computing the distance between each finger movement, activity patterns were pre-whitened using the covariance matrix of the residual of the General Linear Mode (GLM). Then the crossnobis Mahalanobis distance was computed using a leave-on-out cross validation scheme with the following equation:

$$\mathbf{Dist_{j,k} = (d_j - d_k)\Sigma^{-1}_{res}\,(D_J - D_K)^T/P}$$

Where the distance between condition j and k ($Dist_{j,k}$) is computed by the difference between activity pattern in condition j (d_j) and condition k (d_k), multiplied by the covariance matrix of the GLM residuals (Σ^{-1}_{res}), multiplied by the difference between the condition j (D_J)and k (D_K) of the reaming experimental runs. The resulting values have been normalized on the number of the voxel composing the ROI (P). Following this procedure, we were left with 10 unique values representing the distance between each finger pair without repetitions. To analyze if there is a consistent pattern across representation matrices, we calculated the distance between

each difference displayed in the matrices. This way, if there is a distinct pattern to the representations that can be seen across participants, the differences between each distance should be similar in the different representations. Assuming that fingers that are closer together have more similar representational values due to their functionality and location in anatomical space (Ejaz et al. 2015), we predicted increasing dissimilarity values as the distance between two fingers increased. For example, we predict the difference between the thumb and index to be the same as the difference between the index and the middle because both pairs are equal in distance between the digits (zero). However, we expect the dissimilarity difference between the thumb and index to be *less than* the difference between the thumb and the ring finger due to different distances between the digit pairs (zero versus two). Additionally, this calculated set of differences should be greater than zero due to the functional organizational pattern, otherwise if the pattern is random, we should get values close to zero.

RESULTS

In a preliminary study previously conducted in the Medina lab with the same patient database, fMRI images were collected during a basic fist-release task, in which patients would curl their five fingers into a fist and then extend their fingers out, for both the paralyzed and unaffected hand. Single contrasts of movements vs. rest were computed, in which activation for ipsilesional motor cortex was present during "movements" of the paralyzed limbs. This activity is what led us to ask specific questions about the nature of the activation, given that it was so strong. Figure 4 shows the motor activity during the respective hand movements. As shown in the images,

there was a large area of significant activity within the damaged hemispheres for paralyzed limb “movements”.

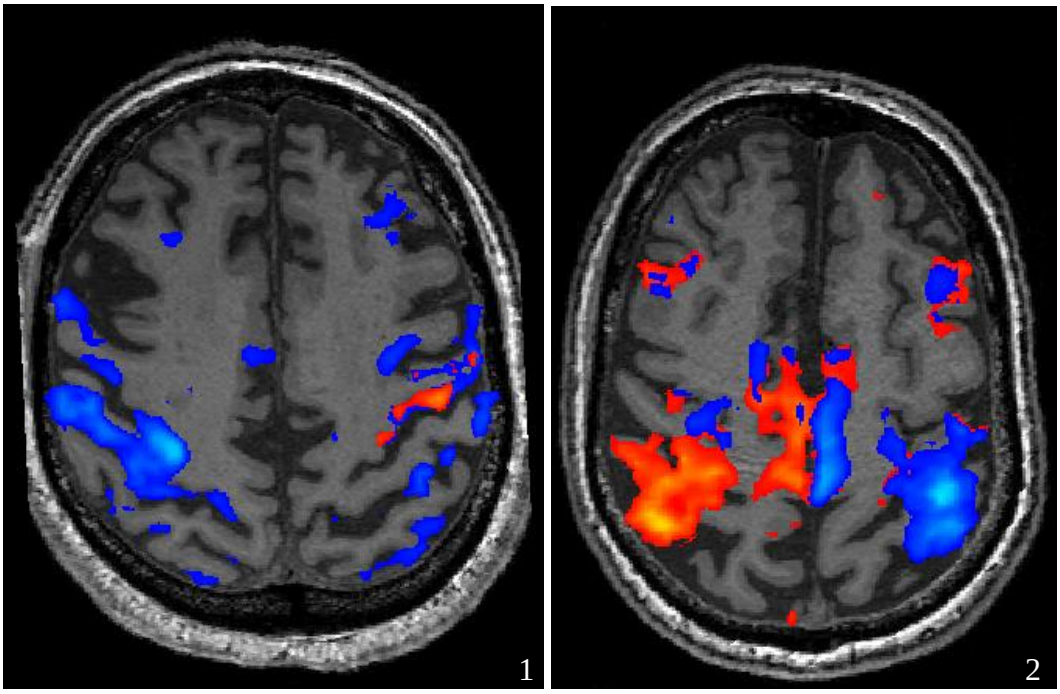


Figure 4 Previously collected functional activity for rest vs movement contrast in the two patients tested. The left image labeled 1 is for patient 1, and the right image labeled 2 is for patient 2. The images shown are in anatomical display (flipped L and R). The red activity in both images is activity for the paralyzed limb during movements (Patient 1: right hand, Patient 2: left hand), while the blue activity is during intact limb movements. The threshold values are at Bonferroni corrected values of 5.5.

After doing RSA on the task specific individual digit movements in these two participants, we are left with dissimilarity matrices detailing the relationships between each digit’s activation pattern’s in both the intact and affected hands in different parts of the brain (detailed in the section above). The dissimilarity matrices we were

interested in were the contralateral representations of the patient's hands in M1 and S1, that is, their left hand in their right hemisphere and their right hand in their left hemisphere. As the matrices below show, there is a specific relationship between digits, showing that fingers further apart from one another are more dissimilar than fingers closer to each other. To address whether or not these representations are organized as opposed to random, we calculated the difference between difference scores between paired fingers. We compared pairs of fingers using a "reference" finger. The first pair would be the reference finger and a digit "x" fingers away from it, and the second pair would be the reference finger and a digit "x+2" fingers away from it. For example, if the thumb finger is the reference finger, we would compare the dissimilarity score of the thumb finger/ring finger pair (three digits away) to the dissimilarity score of the thumb finger/ pinky finger pair (four digits away). Importantly, given that fingers that are farther away should have more dissimilar representations, we expect that dissimilarity values for a finger pair that is more distant would be greater than values for a finger pair that is closer together. Furthermore, all of the pairs entered with the same reference finger had a "finger distance" between the two pairs of exactly one. This way, we are "matching" the reference finger for the pairs that we are comparing to see how the dissimilarity value differs as a function of finger distances. This left us with nine values of difference between each digit pair (shown in Figure 5), all nine of which we then compared to zero (in a one-sampled t-test) to assess whether or not there is an organizational pattern. Again, we expect that dissimilarity values for a pair of fingers that are more distant would be greater than dissimilarity values for fingers that are closer together.

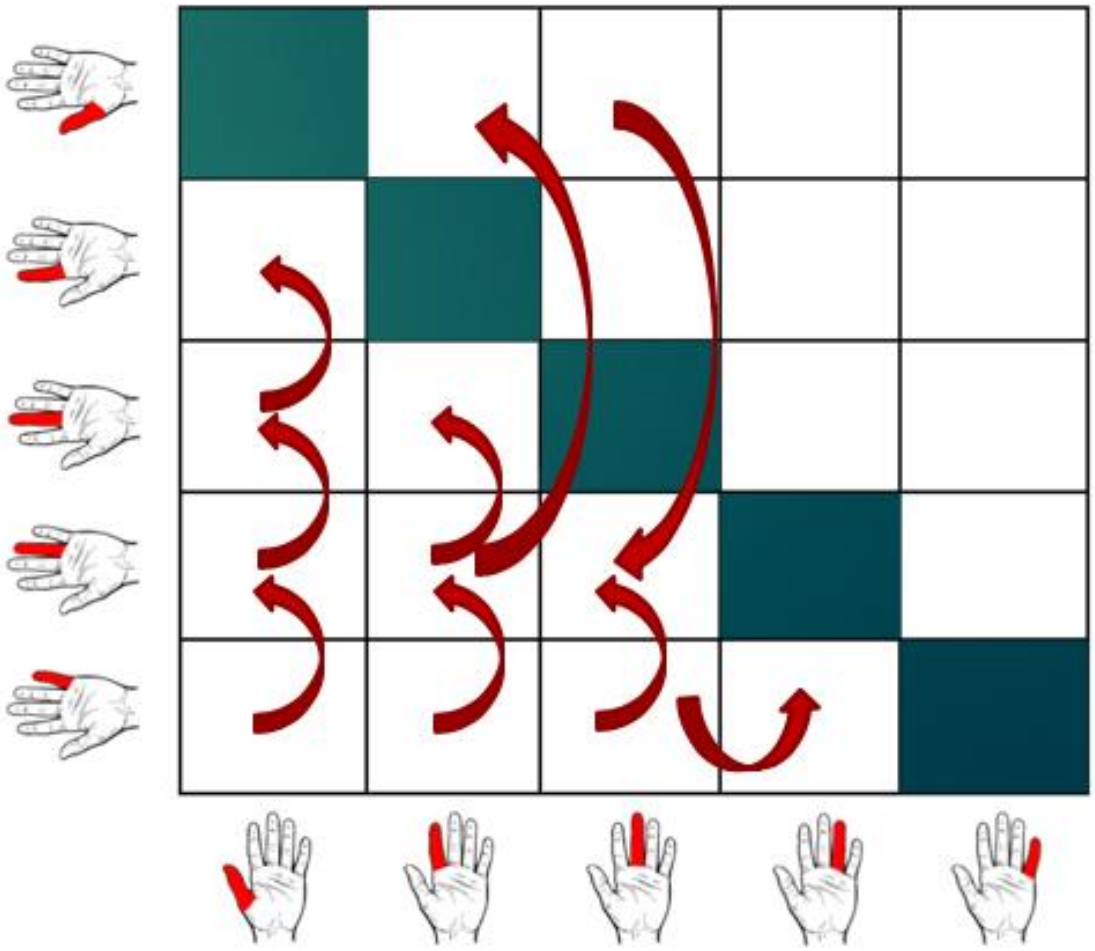


Figure 5 Shows the nine different comparisons done between dissimilarity values of digit pairs. The direction of the arrow shows the direction of subtraction, for example, if the arrow starts in thumb/pinky cell and ends in thumb/ring cell, the subtraction was between the dissimilarity values of thumb/pinky minus the dissimilarity values of thumb/ring. Written out, all of the comparisons done were: Thumb/pinky minus thumb/ring, thumb/ring minus thumb/middle, thumb/middle minus thumb/index, index/pinky minus index/ring, index/ring minus index/middle, index/ring minus index/thumb, middle/pinky minus middle ring, middle/thumb minus middle/ring, and middle/ pinky minus ring/pinky.

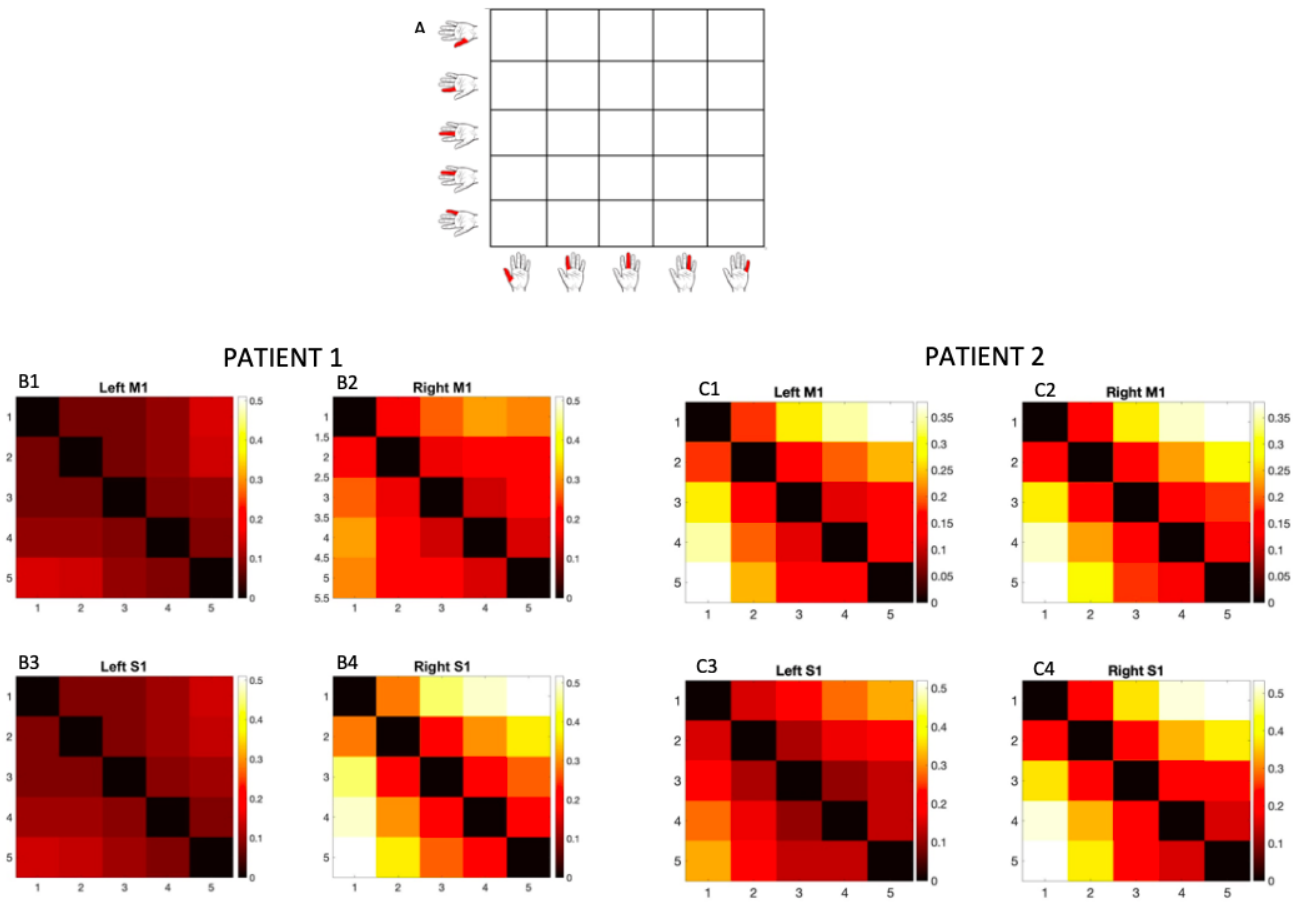
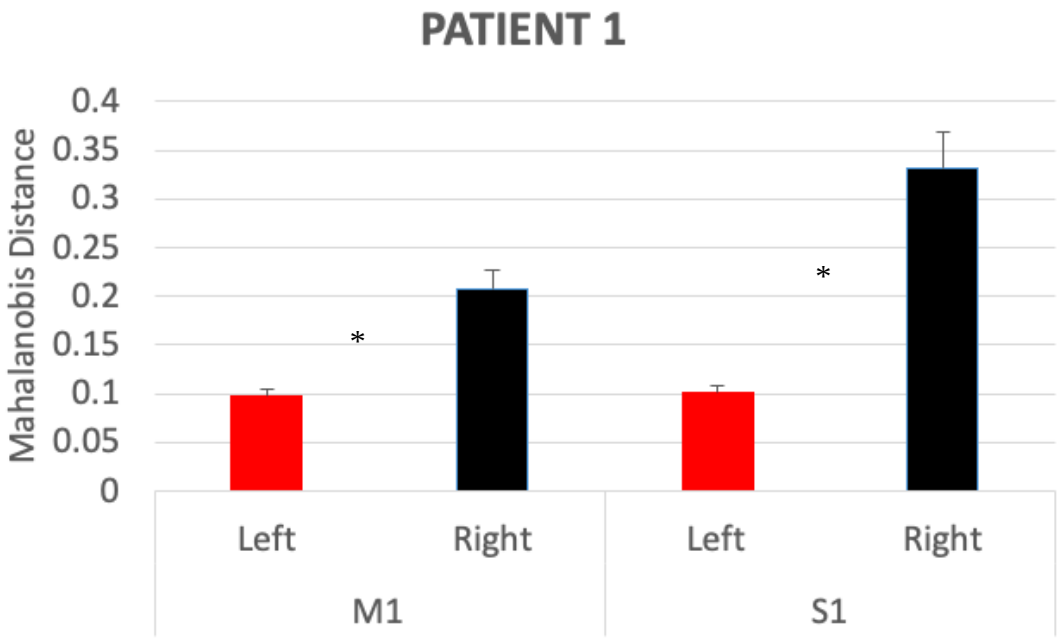


Figure 6 **6A**: Empty matrix showing the layout of which subsequent matrices follow in terms of which digits correspond to which numbers on either axis. Since trials on the right hand were conducted palm face up, we transformed the data to read from thumb to pinky (as shown in the layout), so that the matrices were consistent. **6B**: Patient 1 RSA matrices for contralateral hands. **B1** shows the right (paralyzed) hand in the Left M1, and **B2** shows the left (intact) hand in Right M1. **B3** shows the right (paralyzed) hand in Left S1, and **B4** shows the left (intact) hand in Right S1. **6C** Patient 2 RSA matrices. **C1** shows the right (intact) hand in Left M1, and **C2** shows the left(paralyzed) hand in Right M1. **C3** shows the right (intact) hand in Left S1, and **C4** shows the left(paralyzed) hand in Right S1.

The values of dissimilarity were found between each pair of digit movements (9 unique values detailed in the previous paragraph), and then compared against 0 using a one sample t-test, results of which are shown in Table 2 below. Seeing that difference values in the ipsilesional hemisphere for both patients 1 and 2 were found to be significant ($p < .05$), activation patterns in both ipsilesional M1 and S1 during paralyzed limb "movements" are shown to represent the damaged hand. Furthermore, Figure 6 shows the comparisons of the strength between representations in each patient's contralateral M1 and S1, and Table 3 shows statistics for these comparisons after a paired sample t-test between the 10 values in each of the matrices compared. The differences in strength of the hand representations between the contralesional and ipsilesional M1 for both patients are significant, as were the differences between hemispheric representations in S1.

	CORTEX	HAND	T VALUE	DOF	P VALUE	LLCI	ULCI
PATIENT 1	M1 LEFT	Right	-4.088	8	0.003	-0.0351	-0.0098
	M1 RIGHT	Left	-2.955	8	0.018	-0.0784	-0.0097
	S1 LEFT	Right	-4.632	8	0.002	-0.0274	-0.0092
	S1 RIGHT	Left	-3.395	8	0.009	-0.1487	-0.0284
PATIENT 2	M1 LEFT	Right	-3.717	8	0.006	-0.0919	-0.0215
	M1 RIGHT	Left	-5.712	8	0.000	-0.0927	-0.0394
	S1 LEFT	Right	-4.205	8	0.003	-0.0749	-0.0218
	S1 RIGHT	Left	-5.260	8	.001	-0.1461	-0.0570

Table 2 Statistics from one sampled t-test against 0 for each representation in the respective brain regions. Significance values are shown in red and indicate statistical difference between the differences in individual digit pairs and 0.



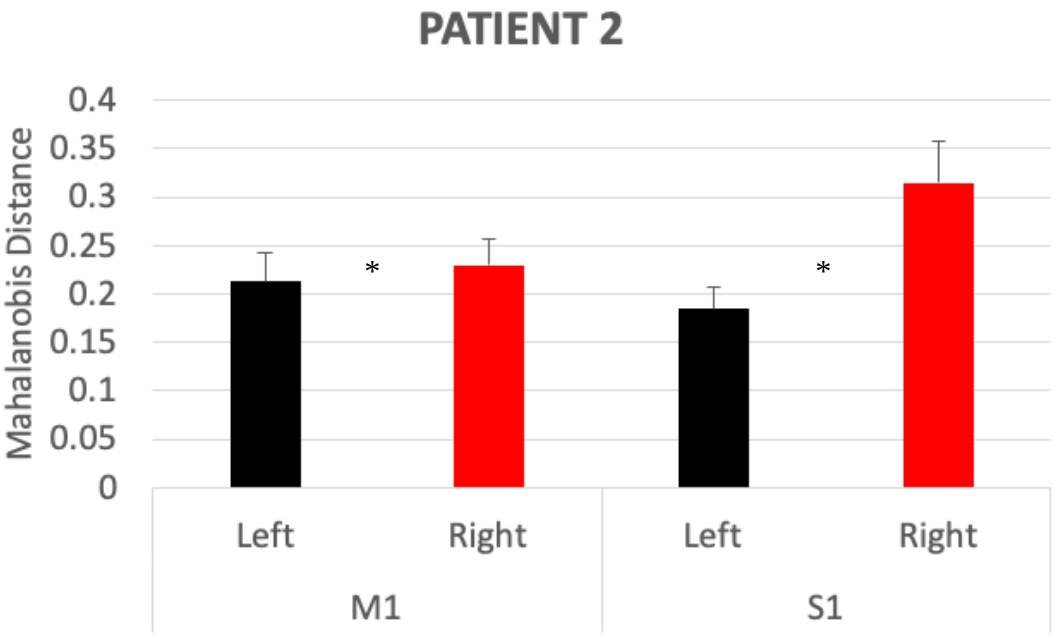


Figure 7 Comparisons between contralateral representations of both patient's hands in M1 and S1. Left and Right labels indicate hemispheres. Black bars indicate intact hemispheres, and red bars indicate lesioned hemispheres. Star between bars indicates significant differences between the strengths of the indicated representations. Standard error bars are displayed on top of each bar.

		LLCI	ULCI	T VALUE	DOF	P VALUE
PATIENT 1	M1 left vs M1 right	-.14977	-.07243	-6.499	9	<.001
	S1 Left vs S1 Right	-.30524	-.15327	-6.825	9	<.001
PATIENT 2	M1 left vs M1 right	-.03308	-.00047	-2.327	9	.045
	S1 Left vs S1 Right	-.17826	-.0836	-6.258	9	<.001

Table 3 Statistics from paired t-test between hemispheric representations in M1 and S1 for both patients as seen by comparing the 10 individual values in both matrices. Significant values indicated in red.

DISCUSSION

We investigated whether the detailed inter-digit hand representation is preserved in stroke patients with CST lesions. Using fMRI, we collected functional data during initiated hand movements of patients paralyzed and non-paralyzed hands. To measure the extent of retained hand representation, RSA was used to decode the specific pattern of and relationship between the functional activity during digit movements in both contralateral M1 and S1. What we found is that, years after

paralysis, the representations of damaged limbs are consistent with those of the intact limbs in both patients.

The organizational patterns of the representation matrices for paralyzed hands in patients contralateral M1's are statistically different from 0 (as seen in Table 2), indicating a non-random representation. A visual inspection of the data suggests that fingers that are closer to one another (e.g thumb and index) are represented more similarly than fingers that are further apart (e.g thumb and pinky). This pattern is consistent with previous findings on the functional organization of the hand in M1 and S1 (Ejaz et al. 2015). Our data reflect a decodable pattern of hand representation for the paralyzed limb in the ipsilesional cortex of the two patients. Shown using RSA, the organizational layout of the neural activity in the contralateral M1 of the patients damaged limb is no different from that of the organization in the unaffected hemisphere. This is evidence that, after years of paralysis, stroke patients maintain representations of their paralyzed hands in their ipsilesional motor cortex in a similar manner they do their normally functioning hands. Plastic changes that could have taken place to repurpose the hand area for other information seem to have not occurred, revealing the importance of the hand representation given that, years after damage, the representation still has the same inter-digit relationship portrayed in normally functioning hands.

While Patient 1 still shows specificity in their affected M1 for their paralyzed hand, it should be noted that it is not as strong as the same representation is for patient two. This could be due to a number of variables, including how much the affected limb was used before damage, which may have impacted the extent to which the representation persists. Makin et al. 2013 show that representations of the intact hand

are increased in amputees who use their intact hand more than their residual hand. It could be that Patient 2 attempts to use their paralyzed hand in ways that are in turn maintaining a representation for it, even though it is not able to move. Furthermore, the difference in the strengths of the contralateral representations in M1 for Patient 1 was significant (p=<.001)and indicated a stronger representation for the intact (left) hand (mean= .208, standard deviation =.059) in the damaged hemisphere when compared to the damaged (right) hand (mean=.097, standard deviation =.027) in the unaffected hemisphere. These results were expected, given that the function is lost for the paralyzed limb, so there is no reinforcement of the representation from using the hand. Additionally, the contralateral representations in S1 were found to be significantly different from one another in respect to the strength in each hemisphere. For Patient 1, the representation of the damaged (right) hand in the contralateral S1 (mean =.106, standard deviation =.021) was found to be statistically different (p =.<001) than the representation of the intact (left) hand in the contralateral S1 (mean =.331 , standard deviation =.118). This is again expected, since the of the right hand is lost, we predicted to see a decreased representation in comparison to the intact hand.

However, Patient 2 shows the opposite; a stronger representation (p =.045) of their *damaged* (left) hand in their contralateral M1 (mean =.229, standard deviation =.088) when compared to the representation of their intact hand in the contralateral M1 (mean =.213, standard deviation =.093).It should be noted that this significance is very borderline, especially given that the difference between the average for left M1 and right M1 is low (.016) Furthermore, the pattern is the same in S1; the representation of the damaged(left) hand in their contralateral S1 (mean =.315, standard deviation =.133) was stronger than the representation of their intact hand in

the contralateral S1 (mean = .184, standard deviation =.134). This increased representation of the damaged hand in both M1 and S1 could be due to a vivid sensory experience from being asked to "move" their paralyzed limb. Patient 2 shared that they felt as though they could actually move their fingers during the trials. This sensory experience may have contributed to the strong representation we see in comparison to the intact hand, given that it is an unordinary task to be asked to do. Since the patients most likely are not asked to try and move their paralyzed limb often, the novel experience of having felt this movement may have evoked a strong sensory experience that is different from the more common sensation of moving their intact limb. Additionally, given that our sample size is small (n=2), it is possible that the significance values from the t-tests are indicating false positives due to a low power of the test. We could run a multiple comparison correction to see if the significance value survives. The p value for the difference between hemispheric representations in M1 is just barely under .05, which may indicate that with more correction, a higher sample size, and a higher statistical power, the value may not be significant. Moreover, a larger sample size is needed to examine whether or not this result lasts across participants, and if so, it should be looked into more.

Interestingly, when analyzing previously collected data on tactile localization in both Patient 1 and 2, Patient 1 was unable to feel any of the 40 trials on their paralyzed hand. However, Patient 2 was able to feel 25 out of the 40 trials on their paralyzed hand, and 26 out of the 40 trials on their intact hand. This reveals that their sensory experience may not be completely lost from the paralysis and may explain why we see such a strong ipsilesional S1 representation. Additionally, compensatory plasticity of the damaged hemisphere may have taken place in attempts of making up

for the loss of function in the limb. This overcompensation has been seen before (Favre et al. 2014) and was actually shown to signal better motor recovery after stroke. In both cases, it is expected that the patients have significant lasting representations in their contralateral S1, because their sensory cortices are not impacted by their lesions. Furthermore, the lasting representation of a detailed hand organization in S1 is consistent with new findings on amputees (Bruurmijn et al. 2017) in which attempted movements of the phantom limb were successfully decoded from S1, which also raises new questions on the importance of sensory information in maintaining these lasting representations.

While some literature suggests plastic changes inevitably take place after a traumatic event to the brain (stroke, amputation), our results suggest that hand representations are maintained in the damaged hemispheres of hemiparetic stroke patients. As the RSA matrices reveal, hand representations for the paralyzed limb in the ipsilesional cortex are consistent with the representations of the intact limbs in the contralesional cortex in both patients. This reveals the importance of the hand representation given that, years after damage, the representation still has specificity between digits (the same specificity portrayed in normally functioning hands). Additionally, we found that S1 carries representations of the damaged hand. Sensory information is important for the experience of movement and seeing that the representation in the contralateral S1 is still present, we can infer that the attempt at moving the paralyzed limb is still initiating an experience of actual movement.

This finding is consistent with newer literature examining how phantom limbs are represented in the brains of amputee patients, showing cortical specificity for the damaged limb (Kikkert et al. 2016). Importantly, the current study suggests that there

may be certain instances in which plasticity does not repurpose cortex after brain damage that contribute to a maintained hand representation in the damaged M1. Since we see lasting representations in the damaged hemisphere years after the limb has been paralyzed, the actual act of movement does not seem to be imperative for these representations to remain. Furthermore, the results of the current thesis compliment the work done in amputees (Wesselink et al. 2019, Kikkert et al. 2016) and give evidence for how peripheral signals are not necessary to maintain the structure and function of the cortex lacking these signals.

In conclusion, our results indicate lasting representations for paralyzed hands in stroke patients with CST lesions. Given that the representations are distinct enough to which each individual digit movement has its own specific activation pattern, new brain-body technology may be able to bypass lesions to the CST and carry the individual signals to the corresponding digits to restore movements to affected limbs. Still, more questions need to be addressed in a larger sample size before this can happen. Specifically, whether or not there is a certain cut-off point (years after stroke) that the hand representation diminishes, or if it stays regardless of the time after damage is an important question to keep in mind. Additionally, more questions pertaining to the specific locations in which these representations are found can be asked, and more analyses can be done to analyze the relationships of the representations between brain regions (M1 and S1), also to investigate how ipsilateral and contralateral representations differ from one another using ANOVA. Moreover, the role of sensory experiences in maintaining representations should be further considered given the evidence from this study and from studies with amputee patients

(Wesselink et al. 2019, Bruurmijn et al. 2017, Kikkert et al. 2016) indicating its contribution to maintaining representations.

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