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Sensory Cortical Re-mapping following Upper-limb Amputation and Subsequent Targeted Reinnervation: A Case Report

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***Abstract*—This case study demonstrates the ability of sensory cortical representations to remap following arm amputation and subsequent targeted reinnervation (TR). Previous human studies have demonstrated functional plasticity in the primary sensory cortex months or years after amputation of the upper arm, forearm, the hand or a single finger, or after subsequent replantation. Targeted reinnervation, a surgical procedure that re-routes inactive, residual sensorimotor nerves previously responsible for innervating the missing limb to alternative muscle groups and skin areas [1-3], has shown the ability to restore a subject's sensation in the reinnervated skin areas. Whether this new technique causes analogous cortical remapping in a similar timeframe as following hand replantation is still unknown. In order to answer this question, high-density electroencephalography was used to study whether the original sensory cortical territory was regained after TR. Before TR, we found that the cortical response to sensory electrical stimulation in the residual limb showed a diffuse bilateral pattern without a clear focus in either the time or spatial domain, Two years after TR, the sensory map of the reinnervated median nerve shifted back to a close-to-normal, predominantly contralateral pattern. The overall trend of TR-induced sensory remapping is similar to previous reports related to hand replantation but occurs over a slower timeframe. This relatively slower progress after TR as compared to after hand replantation could be because TR is performed months or even years after amputation, while hand replantation was performed immediately after the injury. This work provides new evidence for long term plasticity in the human brain.**

I. INTRODUCTION

THE recovery of sensory function in amputated upper limb after re-implantation and repair is the result of functional, biochemical, and cellular events in the peripheral and central nervous systems [4-6]. Many people believe that the level of central nerve system (CNS) restoration determines the effectiveness achieved by a restoring method [7], and maybe because of cortical remapping after amputation, the general clinical outcome after nerve repair in the hand is not ideal yet.

Previous results with regards to sensory remapping following amputation are controversial. On the one hand, qualitative perceptual evidence suggests that maps may remain preserved in the same location, since stimulation of the ends of residual peripheral nerve fascicles can produce localized sensations of the missing limb in amputees [8]. On the other hand, extensive cortical reorganization [4-6] has been described after peripheral nerve injury, represented as a large cortical area being deafferented and followed by adjacent cortical reorganization and contralateral cortical areas taking over the function of the vacant area [4].

Recently, targeted reinnervation (TR), a new nerve repair method, has achieved great success in restoring both motor and sensory function in upper-limb amputee patients. In TR, the residual sensorimotor nerves previously responsible for innervating the missing limb are re-routed to alternative muscle groups and skin areas [1-3]. After several months, new functional connections between the nerves and muscles are created. The reinnervated muscles act as biological amplifiers for efferent motor command signals. Surface electromyographic (EMG) signals at these new sites can then provide control signals for an amputee to operate a motorized prosthesis. TR also can return sensations of touch, pressure, vibration and temperature for the missing limb to the skin overlying reinnervated muscles [9-11]. However, whether TR successfully restores the sensory cortical representation has not been investigated. Therefore, we used high-density electroencephalography (EEG) to identify and quantify cortical activity in response to stimulating different parts of the upper limb during one session before and three sessions after targeted reinnervation surgery in one subject.

II. METHODS

A. Subject

This subject was a 24-year-old male who sustained a traumatic injury and a left trans-humeral amputation in July, 2007. We collected the first set of data before the TR in August, 2008, the week before his targeted reinnervation surgery. During the TR surgery, the median nerve was

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transferred to the motor reinnervation point of the medial head of the biceps; the radial nerve was transferred to the motor reinnervation point of the lateral head of the triceps; and the ulnar nerve was transferred to the motor reinnervation point of the brachialis. Subcutaneous fat was removed over the biceps and triceps to increase the EMG signal magnitude for myoelectric control. This denervated some of his overlying skin enabling hand afferents to reinnervate this skin after several months. Thus when this skin was touched, he felt his missing hand [11]. Three sets of post-TR data were collected after TR in January and July of 2009 and June 2010.

B. Experimental protocol

During all the 4 experiments, the subject was instructed to remain relaxed and to avoid eye movements. We recorded somatosensory-evoked potentials (SEPs) by using sensory stimulation over shoulder, and the residual median nerve in the amputated side (during all the 4 sessions), and shoulder and the middle finger of the intact side (during the 3 post-TR sessions). The both shoulders and middle finger were stimulated via cutaneous stimulation, and the residual median nerve was stimulated using direct nerve stimulation via a needle electrode during all but the last experiment. Because the subject was scheduled for surgery to remove a neuroma two days after the last experiment, we used cutaneous stimulation of his reinnervated median nerve close to the elbow to reduce the risk of infection. When stimulating the reinnervated median nerve site, the subject felt a strong and focused sensation of the tip of his missing middle finger together with faint sensation of his thumb and elbow.

For each site, 2000-3000 trials of SEPs were recorded. During stimulation, 2 or 3 blocks of 1000 constant current square-wave pulses were delivered by a Compex II stimulator (Compex Medical SA, Ecutens, Switzerland), with at least 5 minutes of resting time between each block. Each pulse was 0.3 ms long with interstimulus interval set to 500ms and the intensity was set to the highest amplitude that the subject could tolerate without undue discomfort or pain and without detectable muscle contractions.

C. Experimental data collection

High-density (128 channels) scalp EEG Data were collected at 4KHz. EEG electrode positions and the anatomical landmarks (nasion and two preauricular points) were recorded using a 3D magnetic digitizer (Polhemus, Colchester, VT). The digitized electrode locations were used to co-register the EEG data with the subject's anatomical MRI. T1-weighted MR images were taken with a 3T Siemens MAGNETOM Trio scanner (Siemens AG, Erlangen, Germany) at Northwestern Memorial Hospital. Approximately 176-192 contiguous images in the sagittal plane were taken, with voxel dimensions of 1.0 x 1.0 x 1.0 mm and voxel matrix of 256 x 256.

D. Data processing

EEG signals were screened for the presence of eye and muscle movement artifacts in any of the channels, which eliminated that signal in an individual trial from further analysis. The remaining trials were aligned by the down-phase of the stimulation artifact, segmented, and averaged for each channel in the time window from -20 ms to 50 ms with respect to the down-phase of the stimulation artifact. The averaged EEG signals were imported into the CURRY software environment (Version 5.0, Compumedics Neuroscan, Charlotte, NC) for reconstructing the sensory cortical activity.

In CURRY software, a subject-specific boundary element method (BEM) model was built based on the subject's anatomic MRI data. The BEM model was composed of three compartments for the skin, skull, and brain with 10.0 mm, 9.0 mm, and 7.0 mm resolution, respectively. Coefficients of conductivity used for each compartment were 0.25 S/m for skin, 0.017 S/m for skull, and 1.79 S/m for brain [12]. The input EEG data was baseline (-20 to -5 ms) corrected, and then co-registered to the reconstructed skin by superimposing the locations of anatomical landmarks (nasion and two preauricular points). The Low Resolution Electromagnetic Tomography (LORETA) method was chosen as the inverse method to localize cortical generators from the scalp EEG potentials [13, 14]. The LORETA method with parameter Lp = 1 has been shown to provide better source localization ability than a variety of other inverse methods, including moving dipoles and minimum norm [12, 15, 16]. Current density strengths were measured in units of $\mu A/mm^2$.

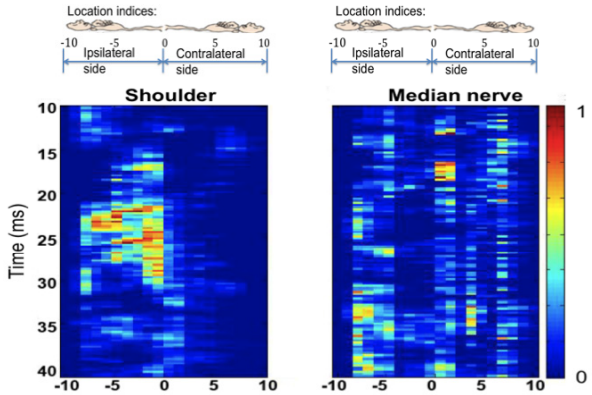
Current density reconstructions exported from CURRY were loaded into MATLAB (The Mathworks, Natick, MA) for further processing and analysis. In Matlab, the region of interest (ROI), consisting of bilateral primary somatosensory cortices (S1) for sensory representations, was manually chosen based on the subject's anatomical MRI data. The MATLAB routine then automatically extracted all sources from the current density reconstructions that resided in this region. Bilateral S1 areas were further divided into segments from medial to lateral, each being 10 mm long. This processing allows us to represent the bilateral S1 using location indices, where -1 to -10 indicate segments on ipsilateral side S1 from -1 cm to -10 cm to the medial line, and 1 to 10 indicate segments on contralateral side S1 from medial to lateral, as shown on the top of figure 1a. Cortical activity on each of these segments was voxel-averaged and normalized to the maximum during the 10 ms to 40 ms window. Using the above method, a time-location distribution of cortical activity on bilateral S1 over 10-40 ms was created.

III. RESULTS

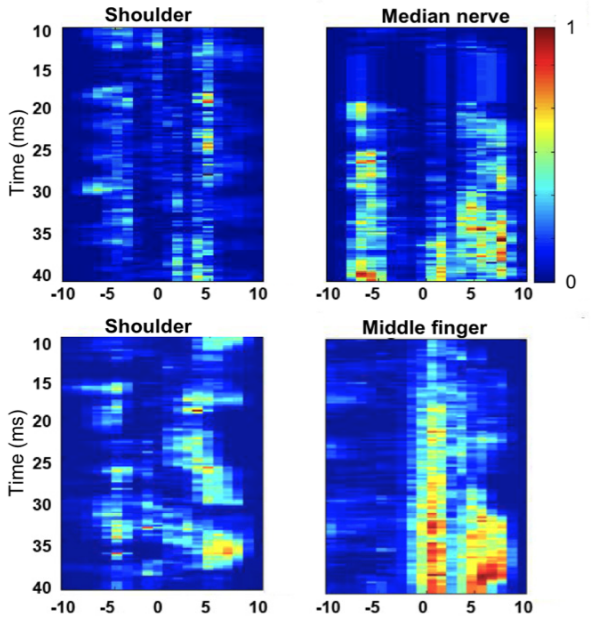
Results of time-location distribution of cortical activity on the bilateral S1 cortices over 10-40 ms from different sites are shown in Figure 1. In this figure, the x-axis consists of location indices, and the y-axis displays the time from 10 ms to 40 ms with 0 representing the down-phase of the stimulation. The color bar on the right side of each of these subplots shows the normalized strength of the cortical

activity. In general, during all of the 3 post-TR experiments, we found that cortical responses to electronic stimulations of the intact side middle finger were located quite consistently on the contralateral primary S1 (indexed as '5' in figure 1b-d) with strong responses delayed about 30ms to the stimulation. This suggested that our methods were able to reliably identify the sensory map of the finger. Surprisingly, we also found that results of stimulating the shoulder from the amputated site varied over different sessions; and showed an ipsilateral mapping before TR. Particular reasons for this variance are not clear at this time.

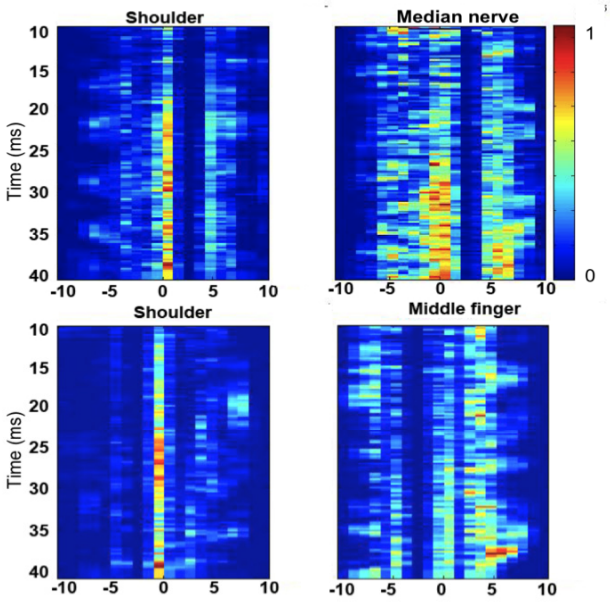
Results obtained before TR by stimulating the residual median nerve from the amputated side showed a diffuse bilateral pattern without clear focus in either time or spatial domains (Figure 1a). Six months and one-year after TR, the responses of stimulating the residual median nerve showed a bilateral spatial pattern on S1, and a focused pattern in the time domain with the strong activity delayed about 25 ms with respect to the descending edge of the stimulation pulse (Figure 1b-c). Two years after TR, we observed even more focused cortical activity in both time and spatial domains (Figure 1d). In this figure, strong activity on contralateral S1 during 30 ms to 40 ms can be seen. Both the location and time delay of this strong contralateral activity are consistent with that obtained by stimulating the intact middle finger. However, in this subplot (Figure 1d for median nerve), we still observe moderate activity from the ipsilateral S1.



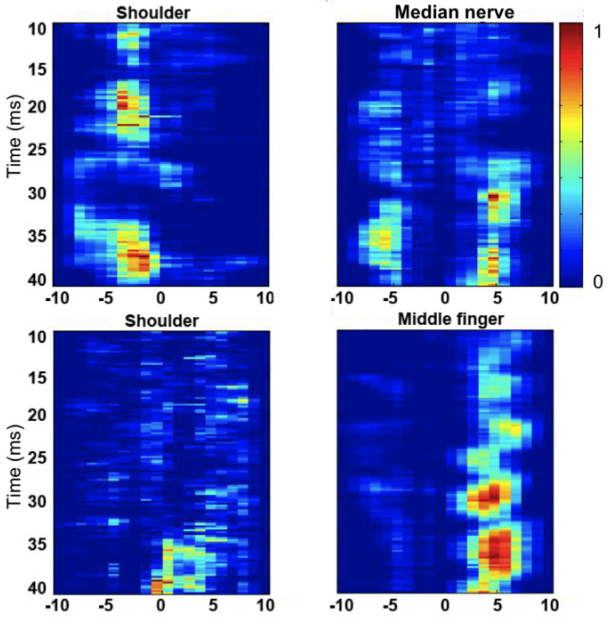
(a) Pre-TR results for the shoulder and the residual median nerve on the amputated left side



(b) *Sensory mapping 6 months after TR for the shoulder and the residual median nerve on the amputated left side (top); and the shoulder and the middle finger from intact right side (bottom).*



(c) Sensory mapping one year after TR for the shoulder and the residual median nerve on the amputated left side (top); and the shoulder and the middle finger from intact right side (bottom).



(d) Sensory mapping two years after TR for the shoulder and the residual median nerve on the amputated left side (top); and the shoulder and the middle finger from intact right side (bottom).

Figure 1. Sensory cortical mapping of different sites of the upper limb following amputation and TR.

IV. Discussions and conclusions

Our results from one individual with a trans-humeral amputation provide a single case study for the long-term plasticity of sensory cortical representations following peripheral injury and targeted reinnervation. About 1 year after amputation, we found that the cortical representation of the residual median nerve shifted and showed a diffuse bilateral pattern without clear focus in either spatial or time domains. This may be due to the reduced sensory feedback from the missing limb to S1.

Focused cortical activity in time domain was first observed 6 months after TR, and then consistently appeared in the results obtained 1 and 2 years after TR. Results of these 3 post-TR experiments showed strong activity on S1 that was delayed about 25 ms from the stimulation, which is in a 'normal' range. This 'returned' focus in the time domain seems to occur earlier than that in the spatial domain.

In spatial domain, we observed a bilateral somatosensory representation evoked by stimulating the residual median nerve from all of the 3 post-TR experiments. However, this bilateral representation broadly covered the cortical shoulder/elbow/hand/finger areas during the first 2 post-TR experiments. This may explain why the subject, in addition to strongly feeling his missing middle finger, also faintly felt his elbow and thumb. Two years after TR, we observed very focused cortical sensory representations on bilateral S1, with strong activity on the contralateral side and moderate activity on the ipsilateral side, all focused on the finger/hand area (indices: -5 and 5), suggesting that sensory representation of the reinnervated median nerve returned to a close-to-normal pattern.

Our results showed similar changes of the spatial pattern as that reported before related to hand replantation. In these previous reports, about 1 month after immediate surgical replantation that repaired the injured nerve, an ipsilateral cortical representation of the missing hand was observed. The sensory mapping of the replanted had was then shifted to a bilateral pattern about 4 months after the replantation, and back to a predominantly contralateral representation about 8 months after the replantation [17].. This suggests that TR has a similar effect on cortical reorganization as immediate replantation. However, the return of a predominantly contralateral representation was about 2 years after TR, which is slower than the progress after hand replantation. The longer recovery phase of sensory representation after TR as compared to after replantation may be due to the fact that hand replantation was performed immediately after injury, while TR was performed one year after amputation in this subject. In the former case, there may not have been enough time between the injury and replantation to generate significant cortical reorganizational changes. However, in our case, we showed that the cortical representation of the missing finger was already difficult to identify in either time or spatial domain. Lastly, our results showed that even over a year after the amputation, the sensory cortex still preserves its plasticity – this means that cortical reorganizational changes following amputation can potentially be reversed following interventional procedures such as TR.

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