New Type of Cortical Neuroplasticity After Nerve Repair in Brachial Plexus Lesions

Roland Beisteiner, MD, MA; Ilse Höllinger, MSc; Jakob Rath, MD; Moritz Wurnig, MSc; Markus Hilbert; Nikolaus Klinger, MSc; Alexander Geißler, MSc, PhD; Florian Fischmeister, PhD; Christian Woiber, MD; Gerhard Kloesch, MSc; Hanno Millesi, MD; Wolfgang Grisold, MD; Eduard Auff, MD; Robert Schmidhammer, MD

Background: In brachial plexus avulsion, a recent technique connects the ending of the disrupted musculocutaneous nerve to the side of the intact phrenic nerve to regain elbow flexion. This requires the phrenic nerve to perform a new double function: independent control of breathing and elbow flexion. Neuroplastic changes associated with acquisition of double nerve functions have not yet been investigated.

Objective: To evaluate neuroplastic changes associated with acquisition of double nerve functions in a mono-functional nerve (phrenic nerve).

Design: Clinical and functional magnetic resonance imaging investigations during arm movements, forced inspiration, and motor control tasks.

Setting: Investigations at the Medical University of Vienna, Vienna, Austria.

Participants: Three healthy control subjects, 2 patients with phrenic nerve end-to-side coaptation, and 1 control patient with C7 end-to-end coaptation (same clinical presentation but phrenic nerve unchanged).

Results: Clinical documentation showed that both patients with phrenic nerve end-to-side coaptation were able to control the diaphragm and the biceps independently via the same phrenic nerve. In contrast to all controls, both patients with phrenic nerve end-to-side coaptation activated the cortical diaphragm areas with flexion of the diseased arm.

Conclusion: Our functional magnetic resonance imaging data indicate that the patient's cortical diaphragm areas reorganize in such a way that independent control of breathing and elbow flexion is possible with the same neuronal population.

Arch Neurol. 2011;68(11):1467-1470

Owing to total paresis of the affected arm, complete brachial plexus lesions represent a seriously disabling neurological condition. In cases of root avulsion, reconstruction of nerve continuity is impossible. To regain at least partial arm functions, nerve fiber transfers that connect axon donors from outside the brachial plexus with the affected plexus nerves are increasingly performed. However, the detailed neuroplastic changes associated with clinical recovery are yet unknown. There are 2 major nerve transfer procedures for restoration of elbow flexion in cases of root avulsion. Nerve fibers from the contralateral healthy C7 root and nerve fibers from the ipsilateral healthy phrenic nerve can be used for reinnervation of the musculocutaneous nerve.2,3 This allows patients to regain elbow flexion of the paretic arm via contralateral C7 inputs or via the ipsilateral phrenic nerve. This technique, called end-to-end nerve repair, has 1 major disadvantage. There is a loss of function in the donor nerve targets: muscles originally innervated by the contralateral C7 root or the ipsilateral phrenic nerve are denervated.

An alternative approach is the nerve fiber transfer using end-to-side nerve repair,4 where the ending of the disrupted nerve is attached to the side of an intact nerve via an epineurial window. Recently, a modified end-to-side procedure has been suggested where a small motor branch is used to restore motor function.5 The major advantage of end-to-side nerve repair is preservation of donor nerve function. In brachial plexus avulsion, the ending of the disrupted musculocutaneous nerve can be attached to the side of the intact phrenic nerve, thereby preserving diaphragm innervation. Such patients represent an interesting new model for neuroplasticity: the same phrenic nerve is required to control breathing and elbow flexion independently. Although neuroplastic changes with brachial plexus injury have already been reported,6,7 the neuroplastic changes associated with acquisition of an additional nerve function are unknown. We hypothesized that cortical phrenic nerve (dia-
Patient 2 was a right-handed man aged 43 years at the time of a traumatic left complete brachial plexus lesion. He had end-to-side coaptation of (1) the ipsilateral phrenic nerve to (2) the musculocutaneous nerve 5 months after trauma. Left elbow flexion was possible against medium resistance at the time of fMRI (7 years after surgery). A general case description including preliminary data analysis is included in the article by Beisteiner et al.8

In both patients with end-to-side nerve repair, the nerve fiber transfer from the phrenic nerve to the musculocutaneous nerve was done using 2 sural nerve grafts coapted end to side to the phrenic nerve and end to end to the musculocutaneous nerve. Every patient provided fully informed consent with a protocol approved by the local ethics committee.

HEALTHY CONTROL SUBJECTS

To be able to compare fMRI findings of the patients’ reorganized nervous systems with unchanged nervous systems, fMRI recordings were also performed in 3 male healthy control subjects aged 42, 27, and 22 years without any history of nervous system disease.

CLINICAL DOCUMENTATION

In the control patient with C7 end-to-end coaptation, chest radiography documented a normal bilateral diaphragm innervation with deep inspiration (Figure 1). Electromyography of the affected biceps muscle demonstrated independence of muscle innervation and breathing (Figure 2A). In patient 1 with phrenic nerve end-to-side coaptation, video recording showed a lack of biceps contractions with deep inspiration or coughing and no change of breathing patterns with elbow flexion. Chest radiography documented bilateral diaphragm innervation with deep inspiration and no elevated diaphragm (Figure 1). Electromyography of the affected biceps muscle demonstrated independence of muscle innervation and breathing.

In patient 2 with phrenic nerve end-to-side coaptation, video recording and fluoroscopy of the thorax showed a lack of biceps contractions with deep inspiration or coughing and a lack of diaphragm innervation with elbow flexion. Chest radiography documented an elevated but innervated diaphragm on the affected side (Figure 1). Electromyography of the affected biceps muscle demonstrated independence of muscle innervation and breathing (Figure 2A). During forced inspiration and coughing, spikes of motor activation appeared in very few parts of the electromyographic recordings.

FUNCTIONAL MRI

Investigations included 4 tasks: (1) elbow flexion of the diseased arm; (2) elbow flexion of the healthy arm; (3) forced abdominal inspiration; and (4) foot flexion on the side of the diseased arm.

Patient 1 with phrenic nerve end-to-side coaptation performed tasks 1 through 4, patient 2 with phrenic nerve end-to-side coaptation and the healthy control subjects performed tasks 1 and 2, and the control patient with C7 end-to-end coaptation performed tasks 1 through 3. Repetitive investigations were performed with 3-T MRI and 7-T MRI (blood oxygen level–dependent gradient echo–echo planar imaging: 34 slices; 128 × 128 matrix; 230 × 230 × 3-mm field of view; generalized autocalibrating partially parallel acquisition factor 2; and repetition time 2500 milliseconds; for 3-T MRI: echo time 35 milliseconds, bandwidth 2220 Hz; for 7-T MRI: echo time 22 milliseconds, bandwidth 1396 Hz). Between 5 and 10 identical runs (blocked design; 4 rest and 3 activation phases; 20
seconds/phase) were performed per task per patient. At least 2 different MRI investigations were performed per patient on different days. The healthy control subjects performed only 1 fMRI investigation at 3 T. Individual data analysis was performed with SPM8 software (Wellcome Trust Centre for Neuroimaging, London, England) (general linear model; uncorrected $P < .001$; technique adapted for pathological brains).

**RESULTS**

Clinical documentation showed that both patients with phrenic nerve end-to-side coaptation were able to control the diaphragm and the biceps independently via the same phrenic nerve: breathing did not change with arm movements (documented by video recording), the affected biceps muscle was not activated with normal breathing (no regular biceps electromyographic activity), and both sides of the diaphragm were innervated during breathing and did not move with elbow flexion (chest radiography, fluoroscopy of the thorax).

The fMRI studies showed bilateral superior activations of the primary motor cortex with forced inspiration (**Figure 3**). In addition, lateralized midline activations were found in deeper slices. These activations correspond to earlier descriptions of diaphragm representations and normal breathing networks. In contrast to the control patient with C7 end-to-end coaptation, both patients with phrenic nerve end-to-side coaptation activated the diaphragm areas with flexion of the diseased arm. Flexion of the healthy arm and foot did not activate diaphragm areas. Figure 3 shows the significant activation of diaphragm areas with diseased arm flexion in comparison with healthy arm flexion. In addition, the primary arm areas were also activated (lateral from diaphragm areas). All patient findings could be replicated intraindividually and interindividually when repeating experiments on different days and at different magnetic field strengths (3 T, 7 T). Elbow flexion in the healthy control subjects only showed arm areas active—no activity was found in diaphragm areas even when lowering the threshold.

**COMMENT**

As demonstrated by the clinical investigations, the 2 patients with phrenic nerve end-to-side coaptation were able to move their diseased arm independently from their diaphragm via the same phrenic nerve. With respect to these tasks, they were clinically not distinguishable from the control patient with C7 end-to-end coaptation. However, distinction was possible with the fMRI data, which showed activation of diaphragm areas with breathing as well as diseased arm flexion in the patients with phrenic nerve end-to-side coaptation. As expected, there was no diaphragm area activation in the healthy control sub-
patients with phrenic nerve end-to-side coaptation. The columns labeled “right arm vs left arm” show significant activation differences of right vs left (red) and left vs right (blue). In the patients with phrenic nerve end-to-side coaptation, the diaphragm area is activated only with flexion of the injured arm, not with flexion of the healthy arm. In all controls, arm flexions did not activate the diaphragm area. Forced abdominal inspiration selectively activated the diaphragm area in all subjects (rightmost column, blue activation clusters).

Image 66x519 to 294x747

![Original functional magnetic resonance images showing brain activations in the diaphragm area (circles) in the superior primary motor cortex and in the adjacent arm areas (right hemisphere is shown on the left side. Only primary motor cortex activations are depicted, and colors indicate t value distributions within depicted activation clusters (relative scaling according to local maxima and minima). All images are thresholded at P < .001 uncorrected. Representative slices are shown for the 3 healthy control subjects, the control patient with C7 end-to-end coaptation, and the 2 patients with phrenic nerve end-to-side coaptation. The columns labeled “right arm vs left arm” show significant activation differences of right > left arm (red) and left > right arm (blue). In the patients with phrenic nerve end-to-side coaptation, the diaphragm area is activated only with flexion of the injured arm, not with flexion of the healthy arm. In all controls, arm flexions did not activate the diaphragm area. Forced abdominal inspiration selectively activated the diaphragm area in all subjects (rightmost column, blue activation clusters).

We conclude that specific cortical neuroplasticity provides the neurophysiological basis for rehabilitation after peripheral end-to-side repair. Data from fMRI indicate effectiveness of this surgical procedure. Neurological practice should consider this option for therapeutic handling of complete plexus lesions.

Accepted for Publication: March 25, 2011.

Correspondence: Roland Beisteiner, MD, MA, Department of Neurology, Medical University of Vienna, Währinger Gürtel 18-20, A-1090 Vienna, Austria (roland.beisteiner@meduniwien.ac.at).

Author Contributions: Dr Beisteiner takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Beisteiner, Millesi, Grisold, Auff, and Schmidhammer. Acquisition of data: Beisteiner, Hollinger, Rath, Wurimg, Hilbert, Klinger, Geißler, Wober, Klosch, and Schmidhammer. Analysis and interpretation of data: Beisteiner, Hollinger, Fischmeister, and Schmidhammer. Drafting of the manuscript: Beisteiner, Hollinger, Rath, Wurimg, Hilbert, Klinger, Geißler, Fischmeister, Wober, Klosch, Millesi, Auff, and Schmidhammer. Critical revision of the manuscript for important intellectual content: Beisteiner, Grisold, and Schmidhammer. Statistical analysis: Beisteiner and Fischmeister. Obtained funding: Beisteiner, Auff, and Schmidhammer. Administrative, technical, and material support: Beisteiner, Hollinger, Rath, Wurimg, Hilbert, Klinger, Geißler, Fischmeister, Wober, Klosch, Grisold, Auff, and Schmidhammer. Study supervision: Beisteiner, Millesi, Grisold, and Schmidhammer.

Financial Disclosure: None reported.

Funding/Support: This study was supported by grants P18057 and P23611 from the Austrian Science Fund and by the Ludwig Boltzmann Institute for Experimental and Clinical Traumatology, Vienna, Austria.

![Figure 3](Image)

**Figure 3.** Original functional magnetic resonance images showing brain activations in the diaphragm area (circles) in the superior primary motor cortex and in the adjacent arm areas. The right hemisphere is shown on the left side. Only primary motor cortex activations are depicted, and colors indicate t value distributions within depicted activation clusters (relative scaling according to local maxima and minima). All images are thresholded at P < .001 uncorrected. Representative slices are shown for the 3 healthy control subjects, the control patient with C7 end-to-end coaptation, and the 2 patients with phrenic nerve end-to-side coaptation. The columns labeled “right arm vs left arm” show significant activation differences of right > left arm (red) and left > right arm (blue). In the patients with phrenic nerve end-to-side coaptation, the diaphragm area is activated only with flexion of the injured arm, not with flexion of the healthy arm. In all controls, arm flexions did not activate the diaphragm area. Forced abdominal inspiration selectively activated the diaphragm area in all subjects (rightmost column, blue activation clusters).

REFERENCES