



Research article

Inter-hemispheric plasticity in patients with median nerve injury



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HIGHLIGHTS

- Median nerve injury results in enlarged activation in the ipsilateral SI.
- Ipsilateral SI activation is increased for stimulation of both hands.
- The contralateral SI peak level cluster activity is decreased.
- Event-related or blocked paradigm had no effect on the Laterality index.

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ABSTRACT

Peripheral nerve injuries result in reorganization within the contralateral hemisphere. Furthermore, recent animal and human studies have suggested that the plastic changes in response to peripheral nerve injury also include several areas of the ipsilateral hemisphere. The objective of this study was to map the inter-hemispheric plasticity in response to median nerve injury, to investigate normal differences in contra- and ipsilateral activation, and to study the impact of event-related or blocked functional magnetic resonance imaging (fMRI) design on ipsilateral activation. Four patients with median nerve injury at the wrist (injured and epineurally sutured >2 years earlier) and ten healthy volunteers were included. 3T fMRI was used to map the hemodynamic response to brain activity during tactile stimulation of the fingers, and a laterality index (LI) was calculated. Stimulation of Digits II–III of the injured hand resulted in a reduction in contralateral activation in the somatosensory area SI. Patients had a lower LI (0.21 ± 0.15) compared to healthy controls (0.60 ± 0.26) indicating greater ipsilateral activation of the primary somatosensory cortex. The spatial dispersion of the coordinates for areas SI and SII was larger in the ipsilateral than in the contralateral hemisphere in the healthy controls, and was increased in the contralateral hemisphere of the patients compared to the healthy controls. There was no difference in LI between the event-related and blocked paradigms. In conclusion, patients with median nerve injury have increased ipsilateral SI area activation, and spatially more dispersed contralateral SI activation during tactile stimulation of their injured hand. In normal subjects ipsilateral activation has larger spatial distribution than the contralateral. Previous findings in patients performed with the blocked fMRI paradigm were confirmed. The increase in ipsilateral SI activation may be due to an interhemispheric disinhibition associated with changes in the afferent signal inflow to the contralateral primary somatosensory cortex.

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1. Introduction

Peripheral nerve injury of the hand leads to loss of working capacity and a significant decrease in quality of life [29]. Adult patients regain satisfactory motor function but they never recover their sensory ability. Many patients end up with only protective sensation, with remaining pain and cold intolerance [3,16,23]. The

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main reason for this maladaptive healing process is the misdirection of axons at the suture site, resulting in disorderly signal transduction to the cortex [12]. Attempts have been made to improve surgical techniques to facilitate more accurate neural regeneration, but the results have been discouraging. None of the techniques developed have provided any great advantage compared to the standard method of epineural suture [23], and the strongest predictor for superior outcome remains young age at injury [5,31].

After median nerve injury and suture, the deafferented contralateral cortical area corresponding to the median nerve sensory territory, is subject to well-documented intra-hemispheric plasticity [7,22,26,34] but there is also evolving evidence of inter-hemispheric plasticity [6,11,30]. In normal subjects, median nerve stimulation activates the contralateral primary somatosensory cortex (SI), the secondary somatosensory cortex (SII) bilaterally and a network including the contralateral posterior parietal cortex (PPC), the insula, the posterior midcingulate gyrus (pmCG), the supplementary motor area (SMA), the thalamus and the ipsilateral cerebellum [18]. Additionally, median nerve stimulation causes concurrent deactivation of the ipsilateral SI as indicated on functional magnetic resonance imaging (fMRI) by the *negative* blood oxygenation level-dependent (BOLD) response [15,18]. The negative BOLD signal in the ipsilateral SI is associated with elevated sensory thresholds in the contralateral, unstimulated finger, suggesting a functional correlate for the inhibition of the ipsilateral SI [17]. Conversely, there are studies reporting a *positive* BOLD signal in the ipsilateral SI in response to unilateral median nerve stimulation in normal subjects [19,27]. This may be due to strong inhibition [21], but the relative impact of excitation and inhibition on the BOLD signal remains unclear [20].

In previous studies we found that patients with median nerve injury have greater ipsilateral activation during unilateral stimulation of the median nerve, both upon stimulation of the injured and the healthy hand, compared to healthy controls [11,14]. The tactile stimulation technique was similar in these studies but the fMRI paradigms differed. The study of patients was performed with an event-related stimulation paradigm consisting of single brush-strokes, whereas for the healthy controls the image acquisition was performed during a 30 s block of continuous stimulation. For this reason it was uncertain whether the greater ipsilateral activation in patients was a sign of interhemispheric plasticity in response to the peripheral nerve injury or the result of using different stimulation and acquisition paradigms.

The purpose of the present study was to study inter-hemispheric plasticity in the brain after peripheral nerve injury. In particular our aim was to explore 1) if median nerve injury influences the degree of ipsilateral activation, and 2) if the type of fMRI paradigm (event-related or blocked) affects the degree of ipsilateral activation. The reason for the latter was to enable more conclusive comparisons with previous studies performed with different fMRI paradigms.

2. Method

2.1. Study population

The study included four patients and ten healthy volunteers. The patients had complete unilateral median nerve injury at the wrist repaired with epineural suture at Linköping University Hospital between 2009 and 2012. Age (mean $\pm$ SD) at surgery was 35.8 ± 22.5 years (range 17–62 years) and age at investigation was 39.3 ± 22.9 years (range 19–65 years). At least two years (mean 3.7 years, range 2.4–5.1 years) had passed between injury and examination for all patients, in order to give time for maximal regeneration of the nerve. None of the patients suffered from other

disease or injury that may have affected nervous function. The control group consisted of ten healthy volunteers aged 24.7 ± 4.2 years (range 21–33 years). Hand dominance was established with the Edinburgh Handedness Inventory [28] revealing right-hand dominance in three patients and left-hand dominance in one. Among the control subjects eight had right-hand dominance and two had left-hand dominance. Two of the patients were injured in their left hand and two patients in their right hand. Only one patient was injured in the dominant hand.

The study adhered to the principles set out in the World Medical Association Declaration of Helsinki, and was approved by the Regional Ethics Review Board in Linköping (2013/237–31). All patients and volunteers provided informed written consent.

2.2. Static two-Point discrimination test

Tactile sensation was measured with a static 2-point discrimination (2pd) test, which measures multiple overlapping peripheral receptive fields and the innervation density. 2pd was measured using calipers with blunt pins applied just to the point of blanching in a longitudinal direction perpendicular to the skin (Disk-Criminator, Baltimore, Maryland). The test instrument was randomly applied in two radial and two ulnar positions on the volar side of Digits II–V distal to the distal interphalangeal joint. Testing began with a 5-mm between the two pins of the test instrument and then increased or decreased according to the subject's response: normal (0–5 mm), fair (6–10 mm), poor (11–15 mm), protective (only one point perceived), and anesthetic (no points perceived) according to the norm scale of the American Society for Surgery of the Hand. The threshold was defined as the minimum separation the subject experienced as two stimuli. Measurements were made on both hands for comparison.

2.3. Functional magnetic resonance imaging (fMRI)

Images were acquired on a 3T scanner (Philips Ingenia, Best, The Netherlands). For anatomical imaging, 3D Turbo Field Echo T1 weighted images were acquired with a repetition time (TR)/echo time (TE)/flip angle (FA)/field of view (FOV) 13 ms/6.2 ms/8°/240 mm. Thirty-three slices with a thickness of 3 mm without inter-slice gap were aligned to the orbital-meatus line. The same volume was then examined with an echo planar sequence with the following parameters: TR/TE/FA/FOV of 2000 ms/30 ms/90°/240 mm, matrix size of 80×80 mm, and voxel size of $3 \times 3 \times 3$ mm.

2.4. Stimulation paradigms

2.4.1. Healthy volunteers

Subjects lay supine in the MR scanner. To produce the cortical response, tactile stimulation of the median and ulnar nerve sensory territories, respectively, was applied by means of a pneumatic brush. Tactile stimulation was given to the volar aspects of Digits II–III and Digit V of the right hand, respectively, according to two separate paradigms. During the first 5 min the stimulation was given in a *blocked paradigm* where 30 s of 1 Hz brush strokes were interchanged with 30 s of rest. Subsequently, in an 8 min *event-related paradigm*, single brush strokes were delivered in a pre-randomized sequence with inter-stimulus intervals ranging between 14 and 20 s.

2.4.2. Patients

In patients, tactile stimulation was given both to the healthy and the injured hand on the volar aspects of Digits II–III and Digit V, respectively. To avoid movement artifacts due to prolonged MR examination we chose to use only the *event-related paradigm* for

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