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PO Box 117
221 00 Lund
+46 46-222 00 00

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Normalized activation in the somatosensory cortex 30 years following nerve repair in children- an fMRI study

Anette Chemnitz[a], Andreas Weibull[b], Birgitta Rosén[a], Gert Andersson[c], Lars B. Dahlin[a], Anders Björkman[a]

[a]Department of Clinical Sciences Malmö - Hand Surgery, [b]Department of Medical Radiation Physics and [c]Department of Clinical Neurophysiology, Lund University, Skåne University Hospital, Malmö, Sweden.

Running title: fMRI following nerve repair in children

Correspondence to: Anette Chemnitz, MD, PhD
Department of Hand Surgery
Skåne University Hospital, Malmö
SE – 20502 Malmö, SWEDEN
Tel: + 46 40 331000
FAX: + 46 40 928855
E-mail: Anette.Chemnitz@med.lu.se

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Approval by ethics committee

The study design was approved by the ethics committee of Lund University (Dnr 2009/728) and all participants gave their informed consent. The study conforms to the Helsinki Declaration.

Abstract

The clinical outcome following a peripheral nerve injury in the upper extremity is generally better in young children than in teenagers and in adults, but the mechanism behind this difference is unknown.

In twenty-eight patients with a complete median nerve injury sustained at the ages of 1-13 years (n=13) and 14-20 years (n=15), the cortical activation during tactile finger stimulation of the injured and healthy hands was monitored at a median time since injury of 28 years using functional magnetic resonance imaging (fMRI) at 3 Tesla. The results from the fMRI were compared with the clinical outcome and electroneurography. The cortical activation pattern following sensory stimulation of the median nerve innervated fingers was dependent on the patient's age at injury. Those injured at a young age (1-13 years) had an activation pattern similar to that of healthy controls. Furthermore, they showed a clinical outcome significantly superior (p=0.001) to the outcome in subjects injured at a later age, however, electroneurographical parameters did not differ between the groups. In subjects injured at age 14-20 years, a more extended activation of the contralateral hemisphere was seen in general. Interestingly, these patients also displayed changes in the ipsilateral hemisphere where a reduced inhibition of somatosensory areas was seen. This loss of ipsilateral inhibition correlated to increasing age at injury as well as to poor recovery of sensory functions in the hand.

In conclusion, cerebral changes in both brain hemispheres may explain differences in clinical outcome following a median nerve injury in childhood or adolescence.

Introduction

Age at injury is thought to be the most important factor determining outcome following a peripheral nerve injury in the upper extremity (Allan, 2000; Ruijs *et al.*, 2005; Fornander *et al.*, 2009). The clinical outcome following a peripheral nerve injury in adults is generally poor. While motor function of the hand can become fairly good over time, sensory function is often unsatisfactory, especially in terms of recovery of fine sensory function (Jaquet *et al.*, 2001; Vordemvenne *et al.*, 2007). On the other hand, nerve injuries in the upper extremity in children have a substantially better prognosis concerning the return of sensory function (Frykman, 1976; Allan, 2000; Chemnitz *et al.*, 2013b). Injuries in especially young children show an excellent recovery, whereas those in older children show a more moderate recovery of sensory function (Lundborg & Rosen, 2001)).

Clinical improvement of both sensory and motor function, following a nerve injury and repair in adults and in adolescents, has been shown for a period as long as five years postoperatively (Lundborg *et al.*, 2004). However, it is not known for how long the clinical improvement continues. Furthermore, at present it is not known whether the improved hand function over time and the differences in clinical outcome based on age at injury reflect changes in the peripheral nerve itself (Pestronk *et al.*, 1980; Almquist *et al.*, 1983) or a cerebral adaptability, i.e. plasticity. Previous studies have focused on the short term effects of a peripheral nerve injury in adults showing functional and structural changes in grey and white matter in several cortical areas, mainly contralateral to the injury (Hansson & Brismar, 2003; Taylor *et al.*, 2009). However, the long-term effects in the central and

peripheral nervous systems of a peripheral nerve injury in childhood have not previously been studied.

We hypothesized that the differences in recovery of fine sensory function seen in patients injured in childhood compared to patients injured later in life depend on structural and functional alterations in the somatosensory cortex. Our aim was to investigate the activation pattern in the somatosensory cortex following tactile stimulation of the median nerve in patients operated for a complete median nerve injury at a young age. In addition, we wanted to relate the findings in the central nervous system to clinical outcome, and electroneurographical data from the previously injured median nerve.

Materials and methods

Patients

Twenty- eight patients, 23 male and five female, operated at the Department of Hand Surgery, Skåne University Hospital, Malmö, Sweden between the years 1970 and 1993 for a complete median (n=20) or a complete median and complete (n=6) or partial (n=2) ulnar nerve injury sustained at an age below 21 years participated in the study. Six patients had a complete median *and* ulnar nerve injury all of which had sustained their injury between the ages 13-20 years. The median age at surgery was 14 years (range 1-20 years) and the median time lapse since surgery was 28 years (range 20-39 years). The median age at the follow-up examination was in those injured in childhood (i.e. before 14 years) 33 years (range 24-47 years) and in those injured between the ages 14-20; 47 years (range 36-57 years). In 24 patients, a conventional nerve suture had been performed within 24 hours, whereas four patients had been operated after a delay (minimum 3 - maximum 15 months), using the sural nerve as an interposition graft, due to a defect in the median nerve. In 19 patients, the dominant hand was injured. All patients had associated flexor tendon injury but eighteen patients suffered from vascular injuries as well. All patients had received a similar physiotherapy postoperatively and none of the patients had received any sensory and motor re-education programs because such programs were not routine at the time of injury, as they are today. All patients were healthy at the time of the nerve injury. Two patients had been diagnosed with diabetes at the time of follow-up. A control group with 15 healthy volunteers with no history of nerve injury or neuropathy also participated. The median current age of the control group was 37 years (range 23-55 years).

Patients included in this study have recently been included in a larger study focusing on the clinical outcome (Chemnitz *et al.*, 2013b) and on peripheral nerve regeneration (Chemnitz *et al.*, 2013a).

Functional Magnetic Resonance Imaging

Functional magnetic resonance imaging (fMRI) was performed using a whole body 3 Tesla scanner (Siemens Medical Solutions, Erlangen, Germany) equipped with a 12-channel head coil. An electronically controlled pneumatic stimuli system constructed in-house was used for tactile finger stimulation, as described by Weibull et al. (Weibull *et al.*, 2008). It had eight individually controlled channels, each consisting of a pneumatic valve (Festo, Germany) connected via a plastic tube to a membrane (4-D Neuroimaging, San Diego, USA, area approximately 0.8 cm^2). These membranes were taped to the tips of the thumb, index and middle finger of both hands, stimulating the median nerve. Each patient was instructed to position both arms in the way that was most comfortable with the help of cushions and other supports in order to ensure comfort and minimise induced errors due to motion or fatigue. The sensory stimulation of the three digits was applied simultaneously (1 Hz pulse frequency, 100 ms pulse width, 2.5 bars pressure) in a pseudo-randomised order between the injured and the non-injured hand to avoid temporal bias such as habituation effects and fatigue, alternating between rest conditions with no stimuli and stimulation of one of two nerves (i.e. left and right median nerve). The length of each block was 30 seconds and each of the two nerves was stimulated for four blocks during the session.

Before the functional imaging a high-resolution anatomical scan was acquired (3D – Fast Low Angle Shot, echo time/repetition time = 4.9/11 ms, flip angle = 15 °, resolution = 1x1x1 mm^3,

176 transversal slices oriented to form a plane through the anterior-posterior commissures). Blood oxygen level dependent imaging (BOLD) was then performed using a gradient echo – echo planar-imaging pulse sequence with echo time/repetition time 30/2000 ms, 64 x 64 matrix, 33 slices and 3x3x3 mm^3 voxel size with the same orientation as the anatomical scan. After the scanning session, each patient was asked whether any complications had occurred, in order to ensure the use of proper data and allow data to be excluded on reasonable grounds.

Image processing and analysis

fMRI was used to assess cerebral activation during tactile stimulation of injured and non-injured median nerves in patients with a history of nerve injury (n = 28) as well as in the control subjects (n = 15). The patients with a history of nerve injury were sub-divided into two groups based on age at injury; those injured in childhood (group I, n = 13, range 1-13 years old) and those injured during adolescence (group II, n = 15, 14-20 years old).

The fMRI data was evaluated using Brainvoyager QX 2.2 software (Brain Innovations B.V., Maastricht, The Netherlands). The functional data series were motion-corrected, spatial smoothing was performed using a 6 mm kernel width and subsequently normalized to Talairach space by co-registration with Talairach processed anatomical data (Talairach & Tournoux, 1988). Activation maps were created using mixed effects general linear model. Low frequency modulation was suppressed by including Fourier basis sets below 2 cycles per session in the model.

Activation patterns were evaluated, individually and in the three different groups, i.e. group I, II and the healthy subjects at a false discovery corrected threshold of 0.05. Statistical comparisons between the different groups were also performed within the general linear model at $p < 0.05$. To further examine possible age dependences, cerebral activation during median nerve stimulation was correlated to 'age when injured' and 'age when examined'. Furthermore, cerebral activation was also correlated to 'sensory function', which was assessed using the sensory domain of the Rosen score. When performing group analysis, the activation maps of patients with a left-side nerve injury were flipped in the left-right direction to prevent substantial power loss, a strategy that has been used before (Buhmann *et al.*, 2003). However, since the two hemispheres in a single subject are neither functionally nor anatomically equivalent, the spatial noise may increase. The contribution of spatial noise is however minimized as the data are smoothed individually as well as in a group analysis.

Electrophysiological examination

Sensory and motor electroneurography were performed bilaterally using Nicolet Viking Select® equipment (MFI Medical Equipment, San Diego, USA). Sensory fibres were stimulated in the thumb, index and long fingers for the median nerve. Ring electrodes were placed at the proximal interphalangeal and distal interphalangeal joints for the index and long fingers, and for the thumb, just proximal and distal to the interphalangeal joint. Recording electrodes were placed over the median nerve at the proximal wrist crease. For motor conduction studies, responses from the abductor pollicis brevis muscle were recorded on stimulation at wrist and elbow levels. Amplitudes, conduction velocities and distal motor latencies were measured. The values obtained from the injured side were then expressed as

a percentage of the non-injured side. All electrophysiological examinations were performed by the same technician and evaluated independently by the same neurophysiologist.

Clinical examination

The clinical assessment was carried out using the Rosen score (Rosen & Lundborg, 2003). This diagnosis-specific outcome instrument for use after nerve repair consists of three domains assessing sensory, motor and pain/ discomfort separately. Each domain produces a score 0-1 and the total outcome is expressed as a "total score" of 0-3. The same occupational therapist performed all examinations.

Statistical methods

Statistical data analysis was performed using the SPSS version 18.0 (Statistical Package for the Social Sciences, IBM, New York, USA). The data were tested for normality before analysis of any significant difference. Results are presented as medians (minimum and maximum). A non-parametric test (Mann-Whitney U test) was used to compare the results from the electrophysiological and clinical examinations. The fMRI data was evaluated separately.

Results

Functional Magnetic Resonance Imaging

Stimulation of median nerve innervated fingers resulted in a measurable cortical response in 27 out of 28 patients previously operated for a median nerve injury and in 11 out of 15 healthy controls. The group analysis of group I, II and controls showed that the activation pattern differed depending on the age at injury. Patients who had suffered a nerve injury in childhood (age 1-13 years; Figure 1) showed an activation pattern similar to that of the healthy controls in general, which was characterized by contralateral activation in the primary (S1) and secondary (S2) somatosensory cortex and a deactivation of the ipsilateral S1 as well as in parietal, sensory associated, regions bilaterally and the contralateral hemisphere of cerebellum (Table 1). The ipsilateral deactivation in S1 associated with stimulation of median nerve innervated fingers was located slightly more medially compared to the area of positive activation contralaterally. Patients injured in adolescence, i.e. group II, showed activation of the contralateral S1 and S2, however this activation was significantly larger compared to patients injured in childhood and in healthy controls, presented as between group comparisons in the last two columns of Figure 1. Furthermore, patients injured during adolescence showed a loss of ipsilateral deactivation in S1 and sensory associated regions located in the posterior parietal cortex (Table 1). These differences were statistically significant ($p < 0.05$) between group II and controls as well as between group II and group I, (Figure 1); here presented as positive activation differences bilaterally (due to increased activation contralaterally as well as loss of deactivation in group II). Differences in activation pattern between group I and controls were much more subtle (Figure 1). Notably, these changes were also present when stimulating the healthy median nerve of the opposite hand (results not presented).

Furthermore, cerebral activation following stimulation of median nerve innervated fingers in all subjects were correlated to 'age when injured', 'age when examination' and 'sensory function', the latter examined clinically using the sensory domain of the Rosen score (Figure 2). Interestingly, the older a subject was when injured the larger was the activation of the contralateral S1, and also the larger was the loss of ipsilateral deactivation (correlation coefficient threshold c=0.35). A loss of deactivation along with age at injury also seems to include regions located more rostral bilaterally. Furthermore, the same regions that correlated to age when injured also correlated negatively to the results of sensory domain of the Rosen score, implying a deteriorated recovery of sensory function the older you are when injured. However, no such patterns were evident when correlating to 'age when examined' (Figure 2), ruling out age when examined as a potential bias.

Electrophysiological examination

Sensory amplitudes and sensory conduction velocities for the 28 participants with median nerve injuries are presented in Table 2. The most significant finding was reduced sensory amplitudes in all patients; irrespective of the age at injury, indicating that the peripheral nerve reinnervation was incomplete.

Clinical examination

The results of the clinical examination are presented in Table 2. Patients injured in childhood, i.e. before the age of 14 years, showed a significantly better total score ($p=0.001$) than those injured in adolescence. The superior result of those injured in childhood was seen particularly in the sensory domain ($p<0.001$). Motor recovery was generally good. Patients

that sustained their injury at age 14-20 years had a significantly lower score in the pain/discomfort domain ($p=0.04$) indicating more problems with pain.

Discussion

Here we show that the cortical activation pattern and clinical outcome following a median nerve injury is highly dependent on age at injury. All patients, regardless of age at injury, showed signs of incomplete peripheral nerve regeneration. Thus, the mechanisms behind the difference in clinical outcome seen in the different age groups are likely to be found in the central nervous system.

Following a peripheral nerve injury, some neurons proximal to the injury die and those that survive show a substantial misdirection at the repair site when they re-grow (Hoke & Brushart, 2010) resulting in an incorrect peripheral reinnervation and an altered afferent signal pattern to the brain. All patients in the present study, regardless of age at injury, showed signs of incomplete peripheral nerve regeneration with reduced sensory amplitudes. Such incomplete peripheral nerve regeneration has been shown to result in an incomplete and disorderly representation of the regenerating nerve in S1 in primates (Kaas, 1991).

Here, we show a strong correlation between age at injury and cortical activation in somatosensory areas. Patients injured around adolescence (i.e. 14-20 years) have an increased cortical activation in the contralateral S1 compared to healthy controls, which is similar to what has been described in previous fMRI studies in adult humans with a shorter follow-up (Fornander *et al.*, 2009; Taylor *et al.*, 2009; Li *et al.*, 2011). Taylor and co-workers studied adult patients with median and ulnar nerve injuries, and they showed increased activation in parts of the contralateral S1 (BA 1 and 3b) and decreased activation in other parts (BA 2) compared to healthy subjects (Taylor *et al.*, 2009). All of their patients also had pathological nerve conduction results. It is reasonable to assume that the increased activation is secondary to the changed afferent signal pattern. Interestingly, patients injured

below the age of 14 years displayed a cortical activation pattern similar to healthy controls although their electroneurography indicated incomplete peripheral nerve regeneration with particularly reduced sensory amplitudes. This indicates: 1) that the mechanism behind the observed clinical improvement following a peripheral nerve injury is alterations in the brain and 2) that there are some physiological changes that occur in early adolescence that limits the dynamic potential of the brain.

A central finding of the present study was the differences found in the effects of a median nerve injury on the ipsilateral hemisphere. The changes presently described in the ipsilateral hemisphere have not previously been reported in patients with a peripheral nerve injury. The cortical area, which was deactivated in the younger group and in the healthy subjects, was located in the S1. However, these areas were located slightly more medially than the normal contralateral activation seen following sensory stimulation of the median nerve. This area could correspond to BA 2; an area known to have bilateral hand representations in the S1 (Iwamura *et al.*, 1994; Iwamura, 2000). Unilateral cutaneous stimulation of the hand in healthy humans has been shown to result in a negative BOLD signal and a reduced cerebral blood flow (Hlushchuk & Hari, 2006; Schafer *et al.*, 2012) in the ipsilateral S1. It has been proposed that the negative BOLD signal represents an active synaptic interhemispheric inhibition between the primary somatosensory cortices (Ragert *et al.*, 2011), possibly via the corpus callosum. Clinically, this is noted as an increase in the perception threshold in the ipsilateral fingers during concomitant stimulation of the contralateral median nerve (Schafer *et al.*, 2012). However, the physiological meaning and the exact mechanisms of this ipsilateral inhibition are not completely understood. One possibility for the observed

differences in ipsilateral activation could be that the lack of deactivation, and even activation, of the ipsilateral S1 seen in the adolescent groups might represent a compensatory mechanism. The normal interhemispheric inhibitory action between homologue areas is modulated, perhaps by higher order centres, recruiting areas ipsilateral to the injury in order to better process the signal pattern from the injured nerve. Interestingly, this pattern is also seen when stimulating the median nerve of the uninjured hand, which further shows the extensive dynamics between the hemispheres.

The brain has a tremendous capacity to change and adapt, i.e. plasticity. However, the possibilities and the mechanisms of plasticity may vary with age and it is believed that they decline throughout the age span (Pascual-Leone *et al.*, 2011). In this study we present evidence that functional changes of cortical activation following peripheral nerve injury are dependent on the age when injured, which are also coupled to the extent of recovery of sensory function later in life (Figure 2 **correlations**). We show that already around the age of 14 years, the clinical outcome and the cerebral changes are already similar to those seen in adults. This could be explained by several mechanisms. Previous studies suggest that a critical time period for the functional development of the inter-hemispheric connections exists and it is believed to lie between the ages of 6 and 12 years (Westerhausen *et al.*, 2010). After this period, the inter-hemispheric communication and interaction might resemble its adult form. Thus, before adolescence, the connections between the hemispheres can adapt to the nerve injury and this could explain the differences in ipsilateral activation seen in our study. In addition, the onset of puberty with hormonal alterations is believed to influence cerebral plasticity (Johnston, 2009; Asato *et al.*, 2010) and

this could also be an explanation for the differences in clinical outcome seen between our study groups.

Our results are limited by the number of patients examined. However, peripheral nerve injuries in the upper extremity are rare in children and there are no prior studies focusing on cerebral changes following nerve injuries in the upper extremity in children. Considering the very long follow-up in this study, we believe that evaluation of 28 patients can give valuable information, despite the small groups. Normal ageing could affect the results of the fMRI investigation and the clinical examination. The median age at the follow-up investigation was 47 years in the older and 33 years in the younger group. However, we could not find any correlation between cerebral activation and age when examined.

The exact mechanisms of plasticity after a peripheral nerve injury remain to be investigated. With a better understanding of the effects of a peripheral nerve injury on the central nervous system and of the dynamics between the hemispheres following such an injury, we might be able to offer new therapeutic strategies for these patients in the future.

References

Allan, C.H. (2000) Functional results of primary nerve repair. *Hand Clin*, **16**, 67-72.

Almquist, E.E., Smith, O.A. & Fry, L. (1983) Nerve conduction velocity, microscopic, and electron microscopy studies comparing repaired adult and baby monkey median nerves. *J Hand Surg Am*, **8**, 406-410.

Asato, M.R., Terwilliger, R., Woo, J. & Luna, B. (2010) White matter development in adolescence: a DTI study. *Cereb Cortex*, **20**, 2122-2131.

Buhmann, C., Glauche, V., Sturenburg, H.J., Oechsner, M., Weiller, C. & Buchel, C. (2003) Pharmacologically modulated fMRI--cortical responsiveness to levodopa in drug-naive hemiparkinsonian patients. *Brain*, **126**, 451-461.

Chemnitz, A., Andersson, G., Rosen, B., Dahlin, L.B. & Bjorkman, A. (2013a) Poor electroneurography but excellent hand function 31 years after nerve repair in childhood. *Neuroreport*, **24**, 6-9.

Chemnitz, A., Bjorkman, A., Dahlin, L.B. & Rosen, B. (2013b) Functional outcome thirty years after median and ulnar nerve repair in childhood and adolescence. *J Bone Joint Surg Am*, **95**, 329-337.

Fornander, L., Nyman, T., Hansson, T., Ragnehed, M. & Brismar, T. (2009) Age- and time-dependent effects on functional outcome and cortical activation pattern in patients with median nerve injury: a functional magnetic resonance imaging study. *J Neurosurg*, **113**, 122-128.

Frykman, G.K. (1976) Peripheral nerve injuries in children. *Orthop Clin North Am*, **7**, 701-716.

Hansson, T. & Brismar, T. (2003) Loss of sensory discrimination after median nerve injury and activation in the primary somatosensory cortex on functional magnetic resonance imaging. *J Neurosurg*, **99**, 100-105.

Hlushchuk, Y. & Hari, R. (2006) Transient suppression of ipsilateral primary somatosensory cortex during tactile finger stimulation. *J Neurosci*, **26**, 5819-5824.

Hoke, A. & Brushart, T. (2010) Introduction to special issue: Challenges and opportunities for regeneration in the peripheral nervous system. *Exp Neurol*, **223**, 1-4.

Iwamura, Y. (2000) Bilateral receptive field neurons and callosal connections in the somatosensory cortex. *Philos Trans R Soc Lond B Biol Sci*, **355**, 267-273.

Iwamura, Y., Iriki, A. & Tanaka, M. (1994) Bilateral hand representation in the postcentral somatosensory cortex. *Nature*, **369**, 554-556.

Jaquet, J.B., Luijsterburg, A.J., Kalmijn, S., Kuypers, P.D., Hofman, A. & Hovius, S.E. (2001) Median, ulnar, and combined median-ulnar nerve injuries: functional outcome and return to productivity. *J Trauma*, **51**, 687-692.

Johnston, M.V. (2009) Plasticity in the developing brain: implications for rehabilitation. *Dev Disabil Res Rev*, **15**, 94-101.

Kaas, J.H. (1991) Plasticity of sensory and motor maps in adult mammals. *Annu Rev Neurosci*, **14**, 137-167.

Li, N., Downey, J.E., Bar-Shir, A., Gilad, A.A., Walczak, P., Kim, H., Joel, S.E., Pekar, J.J., Thakor, N.V. & Pelled, G. (2011) Optogenetic-guided cortical plasticity after nerve injury. *Proc Natl Acad Sci U S A*, **108**, 8838-8843.

Lundborg, G. & Rosen, B. (2001) Sensory relearning after nerve repair. *Lancet*, **358**, 809-810.

Lundborg, G., Rosen, B., Dahlin, L., Holmberg, J. & Rosen, I. (2004) Tubular repair of the median or ulnar nerve in the human forearm: a 5-year follow-up. *J Hand Surg Br*, **29**, 100-107.

Pascual-Leone, A., Freitas, C., Oberman, L., Horvath, J.C., Halko, M., Eldaief, M., Bashir, S., Vernet, M., Shafi, M., Westover, B., Vahabzadeh-Hagh, A.M. & Rotenberg, A. (2011) Characterizing brain cortical plasticity and network dynamics across the age-span in health and disease with TMS-EEG and TMS-fMRI. *Brain Topogr*, **24**, 302-315.

Pestronk, A., Drachman, D.B. & Griffin, J.W. (1980) Effects of aging on nerve sprouting and regeneration. *Exp Neurol*, **70**, 65-82.

Ragert, P., Nierhaus, T., Cohen, L.G. & Villringer, A. (2011) Interhemispheric interactions between the human primary somatosensory cortices. *PLoS One*, **6**, e16150.

Rosen, B. & Lundborg, G. (2003) A new model instrument for outcome after nerve repair. *Hand Clin*, **19**, 463-470.

Ruijs, A.C., Jaquet, J.B., Kalmijn, S., Giele, H. & Hovius, S.E. (2005) Median and ulnar nerve injuries: a meta-analysis of predictors of motor and sensory recovery after modern microsurgical nerve repair. *Plast Reconstr Surg*, **116**, 484-494; discussion 495-486.

Schafer, K., Blankenburg, F., Kupers, R., Gruner, J.M., Law, I., Lauritzen, M. & Larsson, H.B. (2012) Negative BOLD signal changes in ipsilateral primary somatosensory cortex are associated with perfusion decreases and behavioral evidence for functional inhibition. *Neuroimage*, **59**, 3119-3127.

Talairach, J. & Tournoux, P. (1988) *Co-planar stereotaxic atlas of the human brain : an approach to cerebral imaging*. G. Thieme;Thieme Medical Publishers, Stuttgart, New York.

Taylor, K.S., Anastakis, D.J. & Davis, K.D. (2009) Cutting your nerve changes your brain. *Brain*, **132**, 3122-3133.

Weibull, A., Bjorkman, A., Hall, H., Rosen, B., Lundborg, G. & Svensson, J. (2008) Optimizing the mapping of finger areas in primary somatosensory cortex using functional MRI. *Magn Reson Imaging*, **26**, 1342-1351.

Westerhausen, R., Luders, E., Specht, K., Ofte, S.H., Toga, A.W., Thompson, P.M., Helland, T. & Hugdahl, K. (2010) Structural and functional reorganization of the corpus callosum between the age of 6 and 8 years. *Cereb Cortex*, **21**, 1012-1017.

Vordemvenne, T., Langer, M., Ochman, S., Raschke, M. & Schult, M. (2007) Long-term results after primary microsurgical repair of ulnar and median nerve injuries. A comparison of common score systems. *Clin Neurol Neurosurg*, **109**, 263-271.

Table 1 - Localization and Talairach coordinates of activated and deactivated clusters during tactile stimulation in patients who have acquired median nerve injury in their youth and healthy controls (please see fig 1 for reference)

	Localization	Talairach coordinates			Activation (+) Deactivation (-)
		x	y	z	
Control group (n=15)	CL S1	-53	-26	47	+
	IL S1	34	-26	46	-
	CL S2	-54	-24	18	+
	Ass	19	-63	53	-
	Cerebellum	-29	-38	-21	-
Median nerve injury ≤ 13y (n=13)	CL S1	-52	-31	48	+
median age when injured = 7 [1-13y]	IL S1*	47	-25	52	-
	CL S2	-53	-23	18	+
	Ass	14	-40	39	-
	Cerebellum	-12	-48	-20	-
Median nerve injury ≥ 14y (n=15)	CL S1	-48	-28	45	+
median age when injured = 17 [14-20y]	IL S1*	51	-38	31	+
	CL S2	-52	-21	16	+
	Cerebellum	23	-48	-28	+

Activation patterns during tactile stimulation of the median nerve in subjects with a median nerve injury, acquired before (n=13) and after the age of thirteen years (n=15) and in control subjects with no history of nerve injury (n=15). Subjects with median nerve injury acquired in childhood (median age at injury = 7 y) presented similar activation pattern in the somatosensory cortex as the control subjects. Specifically, these both groups showed an inhibition of the ipsilateral S1, sensory associated parietal areas and cerebellum, marked with an (-) in the table. In the group where median nerve injury was acquired after the age of thirteen years (median age at injury = 17 y) the ipsilateral inhibition was lost, instead regional positive activation was seen. Coordinates represent 'centre-of-gravity' at $p < 0.001$ [t-value 4.14, 4.32 and 4.14 for the control group, group I and II respectively] (* $p < 0.01$ [t-value 3.05 and 2.98 for group I and II respectively]). CL = contralateral; IL = ipsilateral; Ass = Associated parietal areas.

Table 2

	Age 1-13 years n= 13	Age 14-20 years n= 15	p-value
Total score (0-3)	2.8 (1.8-3.0)	2.2 (0.9-2.6)	**0.001**
Sensory domain (0-1)	0.88 (0.47-1.0)	0.50 (0.18-0.69)	**<0.001**
Motor domain (0-1)	0.96 (0.67-1.0)	0.85 (0.08-1.0)	0.25
Pain/ Discomfort (0-1)	1.0 (0.5-1.0)	0.67 (0.50-1.0)	**0.037**
Sensory Amplitude (0-100 %)	20 (13-73)	26 (0-48)	0.32
Sensory conduction velocity (0-100%)	83 (64-97)	77 (0-88)	0.07

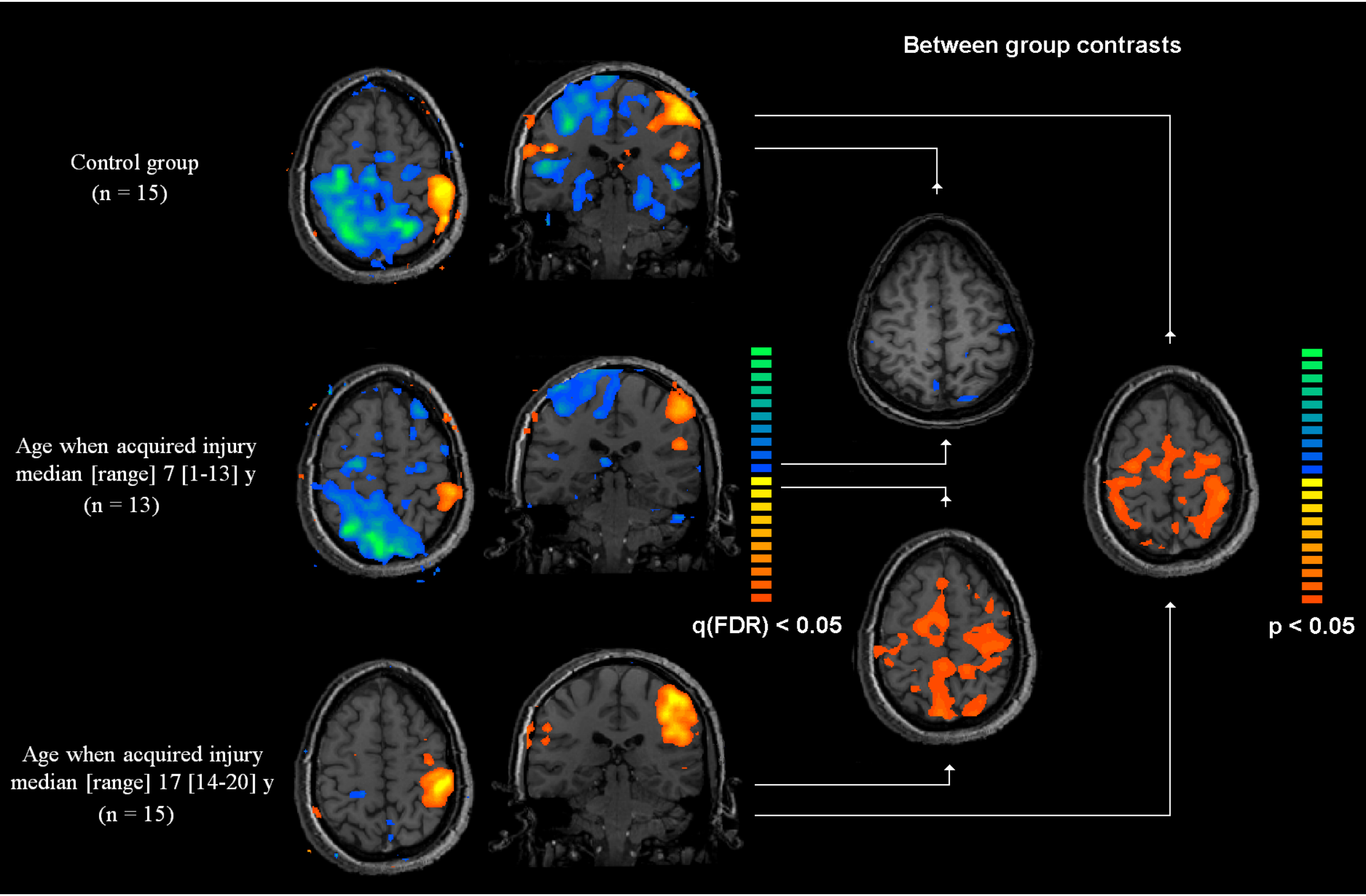
All values are median values (minimum-maximum). Non-parametric Mann-Whitney U tests have been used when comparing the different groups. Each domain of the total score gives a value 0-1 and the maximum total score is 3, representing a normal sensory and motor function without pain or discomfort. Electrophysiological values obtained from the injured side are expressed as a percentage of the un-injured (control) side. Only results for the median nerve are presented. P-value < 0.05 is indicated in bold.

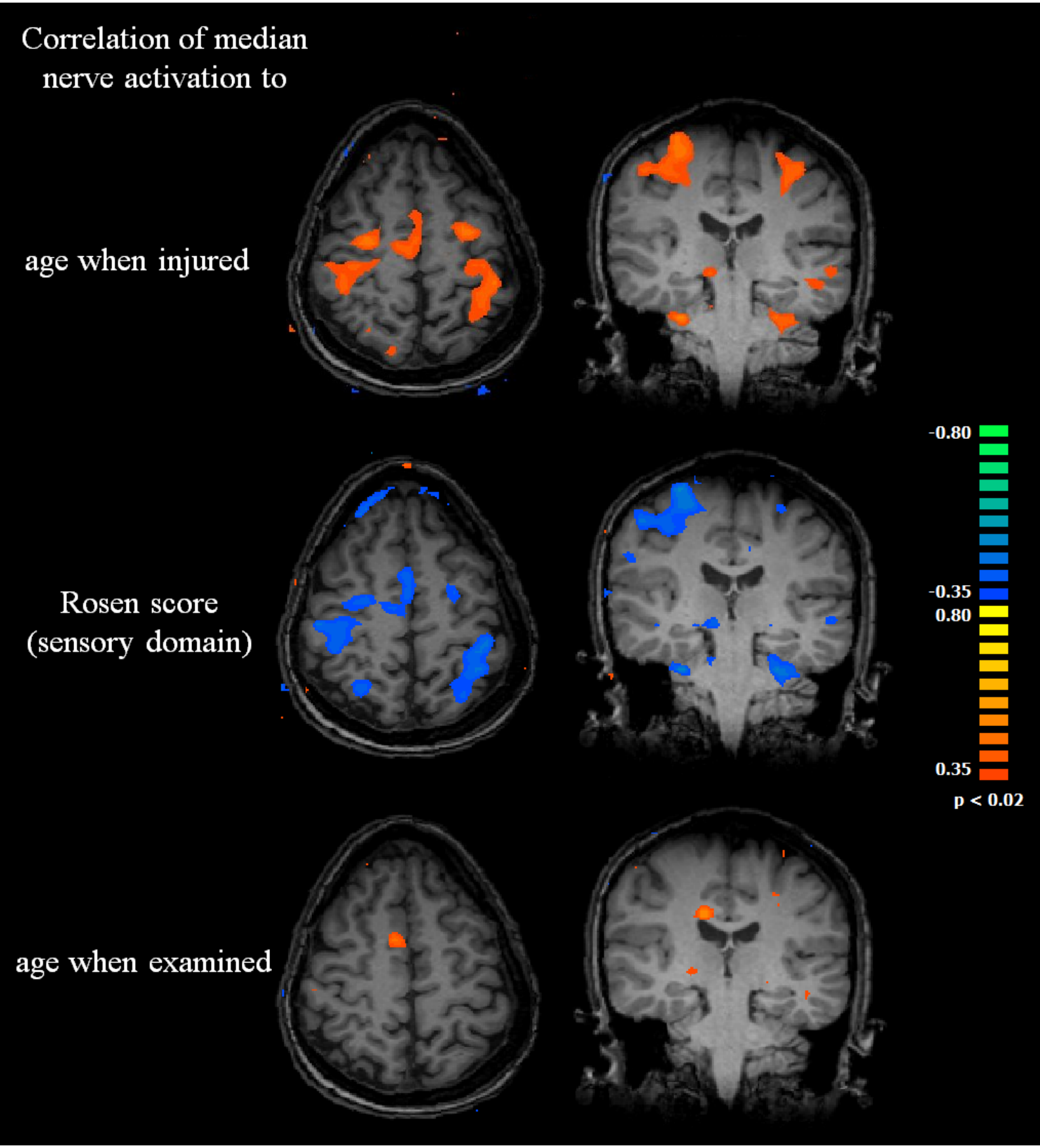
Figure 1 Legend

Figure 1. Column 1 and 2: Healthy controls (first row), as well as patients that sustained a median nerve injury during childhood (group I; second row), present activation in contralateral S1 and S2 and a corresponding deactivation ipsilaterally during tactile stimulation (qFDR < 0.05, corresponding to a t-value of ±3.02 for the healthy controls and ±3.18 for group I). The region of deactivation contains S1 as well as posterior regions of the parietal cortex known as sensory associated areas. Regional activation and deactivation was also present in cerebellum (not shown), see Table 1 for details. In a group of patients that sustained a median nerve injury later in life (group II; third row), i.e. during adolescence, a substantial loss of the ipsilateral and posterior parietal deactivation was evident (qFDR < 0.05, corresponding to a t-value of ±3.78). Column 3 and 4: Comparing group II to I statistically (third column, last row) showed that patients that sustained a median nerve injury during adolescence had an increased contralateral activation in S1 and S2, as well as a loss of ipsilateral deactivation (seen as a positive activation here due to statistical comparison ($p < 0.05$). Similar activation patterns were seen when contrasting group II to healthy controls (column 4), however, these differences were not seen when contrasting group I to healthy controls ($p < 0.05$). Slices are presented at Talairach coordinates z = 51 and y = -31.

Figure 2 Legend

Figure 2. Tactile stimulation of a median nerve injured in childhood or adolescence results in a cortical activation pattern that is dependent on the age when injured (first row). The older a patient was when suffering a median nerve injury the larger is the activation of the contralateral somatosensory cortex and the larger is the loss of ipsilateral deactivation. In addition, these changes are also linked to poor recovery of sensory function (second row). Notably, these results were not biased from the actual age when examined (third row). Correlation coefficient threshold was set to 0.35, corresponding to $p < 0.02$ not corrected for multiple comparisons, in all three tests. Slices are presented at Talairach coordinates z = 52 and y = -23.


Between group contrasts
Control group
(n = 15)
Age when acquired injury
median [range] 7 [1-13] y
(n = 13)
Age when acquired injury
median [range] 17 [14-20] y
(n = 15)
q(FDR) < 0.05
p < 0.05


Correlation of median nerve activation to
age when injured
Rosen score (sensory domain)
age when examined
-0.80
-0.35
0.80
0.35
p < 0.02