Loss of Interhemispheric Inhibition on the Ipsilateral Primary Sensorimotor Cortex in Patients with Brachial Plexus Injury: fMRI Study

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This functional magnetic resonance imaging study verified an antagonistic pattern in which a concomitant deactivation of ipsilateral primary sensorimotor (SM1) was coupled to the contralateral SM1 activation in healthy controls during unimanual hand grasping. Of note, dramatic reduction of ipsilateral SM1 deactivation (loss of antagonistic pattern) was observed during movement of intact hands by patients with unilateral brachial plexus injury. We propose that the disappearance of the antagonistic pattern of SM1 activities in the patients with brachial plexus injury reflects a reduction of interhemispheric inhibition, which may mirror an adaptive mechanism to functional status.

Interhemispheric control of motor areas is important for bimanual coordination and skill acquisition. Such bihemispheric control of motor processes is necessary for asynchronous bimanual movements and to inhibit interference from the opposite hemisphere when even simple unimanual movement is required.[1] Evidence supporting interhemispheric inhibitory mechanisms in humans is mainly from transcranial magnetic stimulation (TMS) studies.[2–5] Nevertheless, TMS may activate interneurons and pyramidal cells simultaneously, so that the effects of TMS cannot be expected to reproduce physiological activation completely (ie, voluntary movement).[6]

Allison and colleagues[7] used functional magnetic resonance imaging (fMRI) to investigate interhemispheric interaction in motor control. Along with cerebral activation of primary sensorimotor cortex (SM1) contralateral to the hand movement, concomitant ipsilateral SM1 deactivation (decreased fMRI-BOLD signal, suggesting a reduced flow and, operationally, a regional net inhibition of neuronal activity[8,9]) was noted in subjects performing finger–thumb opposition tasks. This antagonistic pattern was interpreted as fMRI evidence of interhemispheric inhibition.[7]

We reason that if the ipsilateral SM1 deactivation implicates a functional inhibition in the normal case, a potentially central adaptive modulation in patients with incapacitating injury to major peripheral nerves is a reduction of deactivation in the SM1 ipsilateral to the intact hand during unimanual movement. Operationally, there is no need to inhibit an already disabled arm while moving the intact hand. This hypothesis was tested on 9 patients with brachial plexus injury (BPI) and on 9 healthy controls.

Patients and Methods

Patients

Nine healthy right-handed adults (male = 6, female = 3, 19–24 years old) and 9 right-handed patients with brachial plexus injury (BPI), with an injury history of 3 months to 8 years (male = 8, female = 1, right BPI = 5, left BPI = 4, 20–65 years old) were studied. Patients were free from other central nervous system disease. Neurological and electrophysiological examinations of patients showed injury localizations and extensions varying from C3 to T1, characterized by common involvement of C6 and C7, manifested as a severe disabling of hand-grasping. Patients complained of numbness/tingling and had various degrees of sensory deficit to light-touch and pinprick at the involved area of innervation.

Ethics

Consent for the study was obtained from all participants, with a protocol approved by the institutional Ethics and Radiation Safety Committees.

Task

The motor task consisted of simple self-paced hand grasping at 1Hz. All subjects participated in a short training session immediately before scanning and were under visual observation during the fMRI experiment. Each study began with a resting phase (5 dummy + 10 scans) during which participants performed no voluntary motor activity, followed by 10 scans of unilateral hand fist, using either the right hand (healthy controls) or the intact hand (BPI patients). Alternating blocks were repeated consecutively four times. Partic-

ipants were cued with a gentle touch on the left foot before the first scan of each block (rest, movement), to alert them to the change of conditions.

Functional Magnetic Resonance Imaging

Images were acquired using a 3.0T Bruker MedSpec S300 system (Bruker, Karlsrube, Germany) with a quadrature head. Subjects' heads were immobilized with a vacuum-beam pad in the scanner. Subjects' eyes were closed during the experiment. Functional data were acquired with a T2*-weighted gradient-echo EPI using BOLD contrast (TR/TE/θ = 1,700ms/50ms/90°, the slice thickness = 4mm, interslice interval = 1mm, field of view (FOV) = 250mm, 64 × 64 × 16 matrix). For each slice, 85 images were acquired. Brain signals in the bilateral SM1 were specifically observed. The anatomical images were acquired using a high-resolution T1-weighted, 3D gradient-echo pulse sequence (MDEFT: Modified Driven Equilibrium Fourier Transform; TR/TE/TI = 88.1ms/4.12ms/650ms, 128 × 128 × 128 matrix, FOV = 250mm).

Image Analysis

WITHIN-GROUP ANALYSIS. Data were analyzed with statistical parametric mapping (SPM99 software from the Wellcome Department of Cognitive Neurology, London), running under Matlab 6.0 (Mathworks, Sherbon, MA) on a Sun workstation. Images of right BPI patients (using left hands for the experiment) were flipped[10,11] for a homogeneous motor representation. The first five images were discarded from analysis, to eliminate nonequilibrium effects of magnetization. Scans were realigned, normalized, time-corrected, and spatially smoothed with an 8mm full width at half maximum (FWHM) gaussian kernel, using standard SPM methods.[12,13] Contrasts between movement and rest conditions

$$\text{Activation} = \text{movement} - \text{rest};$$

$$\text{deactivation} = \text{rest} - \text{movement}$$

were examined by voxel-specific t-tests {SPM(t)} across all participants of the same group. t-scores were subsequently transformed to the unit normal Z-distribution to create a statistical parametric map {SPM(z)} for each contrast. Regionally specific differences that survived an uncorrected threshold of $p < 0.001$ (Z = 3.09, with cluster size = 5 pixels) were considered statistically significant. Maxima were localized on the normalized structural images and labeled using the nomenclature of Talairach. Spatial extent (significant voxel numbers) within SM1 (areas 2, 3, and 4) was calculated using Talairach Daemon (Research Imaging Center, University of Texas).

BETWEEN-GROUP COMPARISONS ON IPSILATERAL SM1 ACTIVITIES. The random effect model was exploited to quantify the ipsilateral SM1 activity difference between groups, using a balanced-design approach.[14] In brief, first-order contrast images of the paired conditions (deactivation = rest minus movement) from each subject were processed with a second-order contrast comparison (between groups), to delineate interaction of groups and conditions. This method accommodated randomness in differential responses by comparing mean activation with variability in activation from

Table 1. Brain Activity Changes in the SM1 during Unimanual Hand-Grasping*

Normal Control										BPI Patient									
Activation					Deactivation					Activation					Deactivation				
x	y	z	Z_{max}	Voxels	x	y	z	Z_{max}	Voxels	x	y	z	Z_{max}	Voxels	x	y	z	Z_{max}	Voxels
Contralateral (Lt) hemisphere																			
−28	−32	68	Inf	3776	−36	−28	32	3.97	56	−34	−36	68	Inf	3687	−18	−28	52	3.29	320
−26	−26	68	Inf							−40	−24	64	Inf						
−40	−28	58	Inf							−38	−30	58	Inf						
−54	−2	36	Inf							−48	−20	56	Inf						
−30	−16	52	4.64							−38	−26	52	Inf						
−58	−4	22	3.83							−26	−12	68	7.38						
										−30	−4	64	5.93						
										−58	−26	46	5.80						
										−54	−26	36	3.23						
Ipsilateral (Rt) hemisphere																			
54	−28	48	4.74	161	28	−36	64	6.01	2545	40	−18	62	5.16	269					
58	−12	28	4.11		10	−40	66	5.08		38	−26	64	4.99						
					18	−30	62	4.98		56	−10	46	4.31						
					22	−30	68	4.91											
					36	−24	48	4.77											
					28	−26	50	3.93											
					38	−36	56	3.69											
					30	−24	62	3.61											
					2	−34	68	3.48											
					44	−28	56	3.27											

*Threshold at $p < 0.001$, cluster size = 5; Inf denotes $Z_{max} > 8.0$. Depicts significant cluster peaks within the (de)activated volume(s) in SM1. Stereotactic coordinates of peak activation are expressed in millimeters and refer to mediolateral position (x) relative to midline (positive = right), anteroposterior position (y) relative to the anterior commissure (positive = anterior), and superior-inferior position (z) relative to the commissural line (positive = superior). Voxels indicate the overall spatial extent of SM1 clusters.

subject to subject, hence group to group. The analysis yielded information on the existence of quantitative differences between BPI patients and the healthy controls in terms of movement-related brain activity changes in SM1, as indexed to the resting baseline. Differences were considered significant at uncorrected $p < 0.05$ (Z > 1.75; cluster size = 5). Spatial extent was calculated.

Results

Table 1 and Figure a,b present the grouped results and maps of controls and BPI patients, respectively, using within-group analysis of SM1 activity. In healthy controls, task-related activations were found preponderantly in the contralateral (left) SM1 and slightly/discretely in the ipsilateral (right) SM1. Prominent deactivation was observed in the ipsilateral SM1 of the control group (see Fig a). However, the BPI patients lost ipsilateral SM1 deactivation in the presence of similar contralateral SM1 activation (see Fig b). Table 2 and Figure c show results and statistical maps for between-group comparisons of the ipsilateral SM1 activities. Significant group-condition interaction was detected. The data showed significantly less deactivation in the ipsilateral SM1 in BPI patients compared with healthy controls.

Discussion

Concomitant ipsilateral SM1 deactivation (decreased BOLD response) associated with the contralateral SM1 activation was verified in our healthy controls (see Figure a and Table 1). Our findings are congruent to previous fMRI reports, using more demanding finger–thumb opposition tasks,[7,15] and are corroborated by a combined positron-emission tomography–TMS study in which a negative covariance between the right cerebral blood flow (rCBF) of contralateral primary motor (decreased rCBF) and the TMS-stimulated ipsilateral primary motor cortex (increased rCBF) was observed.[16] The findings from brain imaging studies are further substantiated by electroencephalographic data. Pfurtscheller and colleagues[17] reported that imaging a unilateral hand movement induces an amplitude attenuation of event-related desynchronization in the contralateral SM1, while triggering in parallel a significant amplitude enhancement or event-related synchronization (ERS) in the ipsilateral SM1. The authors interpret the ERS as deactivation or active inhibition of ipsilateral sensorimotor structures for optimal performance of the lateralized task.

These converging findings lend strong support to the theory that interhemispheric inhibition, manifesting an antagonistic pattern of brain activities, is a critical part of the bihemispheric control mechanism for voluntary movement. In this study, the ipsilateral SM1 deactivation (in the context of decreased BOLD, decreased rCBF, and ERS) is interpreted as an expression of ei-
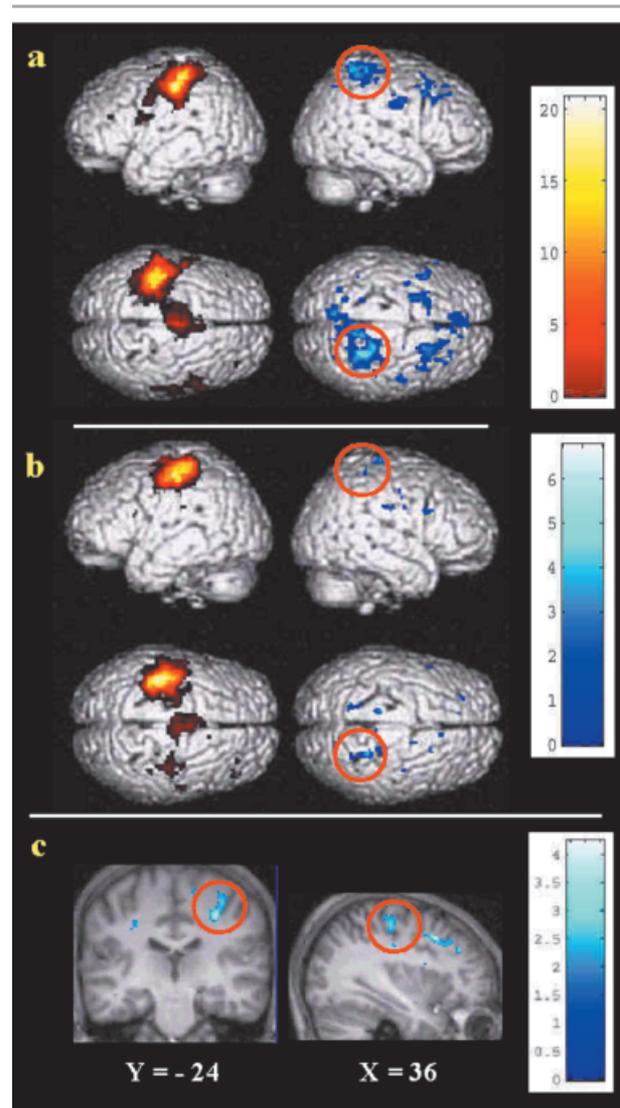

Fig. Maps of brain activity changes in the primary sensorimotor cortices during unimanual movement. (a) Healthy control: activation is seen in the contralateral SM1 with a concomitant deactivation in the ipsilateral SM1 (circled in red). (b) BPI patients: contralateral SM1 activation was similar to that of the healthy controls while the ipsilateral SM1 deactivation was lost. Slight but nonsignificant deactivation was seen. (c) Interaction between groups and conditions: BPI patients manifested significantly less ipsilateral SM1 deactivation (right hemisphere) than healthy controls. Images were displayed at $y = -24$ and $x = 36$ (see annotations in Table 1), respectively, for coronal and sagittal visualizations. In a and b, warm colors (red-yellow) denote activation while the cold colors (blue-cyan) indicate deactivation. Cold colors in c indicate significant interaction (less deactivation in the BPI patients than the healthy controls). Color bars to the right of the images denote the values of Z_{max}.

ther a callosal mechanism of interhemispheric inhibition[7] (cf Reddy et al[15]) or a net inhibition from the orthodromic and transsynaptic input exerted from the

*Table 2. Between-Group Comparisons of Ipsilateral SM1 Activities**

					Rest-Movement (deactivation)					
		Patient < Normal						Normal < Patient		
x	y	z	Z_{max}	Voxels		x	y	z	Z_{max}	Voxels
32	−26	46	3.29	335		54	−14	28	3.19	31
38	−20	36	2.73			48	−24	32	2.06	
30	−30	64	2.73							
38	−22	56	2.59							
16	−26	64	2.38							
10	−40	62	2.34							
24	−32	62	2.01							

*Threshold at $p < 0.05$, cluster size = 5; see Table 1 footnote. Depicts significant cluster peaks within the ipsilateral SM1. Voxels indicate the overall spatial extent of SM1 clusters.

stimulated hemisphere to the other,[16] and, in part, modulated by thalamocortical systems.[17]

The present study provides insightful access to the functional implication of ipsilateral SM1 deactivation through its comparative approach. A dramatic reduction of ipsilateral SM1 deactivation (loss of antagonistic pattern) was confirmed in unilateral BPI patients during movement of their intact hands (see Tables 1, 2, Figure b,c). Differences of SM1 activities between the two groups cannot be ascribed to the performance difference[18] or sensory deficit,[10,11] as all the participants were trained to conduct, using their intact hands, the simple hand-grasping at 1Hz without forceful exertion.

Reorganization in brain motor systems after lesions in the peripheral, as well as in the central nervous system, is well documented.[19,20] The mechanisms underlying the disappearance of the antagonistic pattern of SM1 activities in BPI patients remains to be determined. One plausible explanation is a reduction of interhemispheric inhibition, which could be one facet of overall plasticity of BPI, mirroring the functional status of the patients in an operational context. There is essentially no need for the brain to "inhibit" unlikely potential interference from an already disabled limb. A longitudinal study on a larger group of patients to correlate changes with either the severity of functional impairment or the degree of restitution of function after therapeutic intervention will be heuristic, to explore the origin of these changes and to disclose the unexplored mechanisms of functional plasticity, by penetrating both sides of signal changes observed in functional brain imaging studies.

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Hereditary Motor and Sensory Neuropathy with Minifascicle Formation in a Patient with 46XY Pure Gonadal Dysgenesis: A New Clinical Entity

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This case report is of a patient with 46XY pure gonadal dysgenesis, who presented with chronic progressive motor and sensory polyneuropathy. The sural nerve biopsy exhibited minifascicle formations accompanied by a marked decrease in myelinated fibers. This is the first report of polyneuropathy with minifascicle formations in 46XY pure gonadal dysgenesis. Because a similar polyneuropathy was recently reported in a case with 46XY partial gonadal dysgenesis, it is possible that these cases represent a new type of hereditary motor and sensory neuropathy associated with gonadal dysgenesis.

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46XY gonadal dysgenesis (GD) is a very rare disorder of sexual differentiation, classified as (1) 46XY pure GD, characterized by bilateral streak gonads[1]; and (2) 46XY partial GD, characterized by one streak gonad and a testis. Both are associated with an abnormality of testis differentiation in phenotypic females.

A patient with polyneuropathy with minifascicle formation in 46XY partial GD was recently reported by Umehara and colleagues.[2] Because the case presented a mutation of the human *desert hedgehog* (*DHH*) gene, these investigators suspected that the *DHH* gene might play a critical role in both male gonadal differentiation and perineurial formation. This case report is of a patient with 46XY pure GD with hereditary motor and sensory neuropathy (HMSN), with minifascicle formation. The pathological findings in our case were almost identical to those in Umehara's case, and both cases have consanguinity and GD. Minifascicle formation of the sural nerve is very rare, and only observed in regenerating nerves after transection.[3] Therefore, we considered the possibility that these 2 patients represent a new category of HMSN.

Case Report

This 47-year-old patient was born by normal delivery and raised as a female. Her parents were first cousins; her paternal grandfather and her maternal great-grandfather were brothers. There was no abnormality in her developmental milestones, although she was aware of primary amenorhea from puberty. At age 39, she noticed distal numbness and weakness in all four extremities, which gradually progressed to include distal dominant severe loss of superficial and deep sensation, as well as moderate weakness. She had not noticed bladder dysfunction or severe constipation.

On her first examinations at age 47, her height was 156cm, and her weight 60kg. Her intellect was normal. No abnormality of the cranial nerves was observed. Tendon reflexes were not elicitable. A Babinski sign was absent. Peripheral nerves were not palpable. Sex characteristics included poorly developed breasts and sparse pubic hair. Gynecological examination revealed normal female external genita, a blinded vagina, and an immature uterus. Laboratory examination showed a very high level of LH (29.7mIU/ml; normal: male, 1.8–5.2; female, 1.8–7.6), follicle-stimulating hormone (109mIU/ml; normal: male, 2.9–8.2; female, 5.2–14.4). Her testosterone level was very low (0.04mIU/ml; normal 2.7–10.7) in the serum; estradiol was also low (<10 pg/ml; normal: male, 15–60; female, 25–100). Pelvic magnetic resonance imaging showed bilateral streak gonads. Mature ovary and testis were undetectable. Motor nerve conduction velocity was 37.2m/sec in the median and 32.3m/sec in the tibial; it was not evoked in the peroneal nerve. A nerve conduction block was not observed. Sensory nerve action potentials were not evoked in all examined nerves including the sural nerve. Electromyograms showed neurogenic changes and some denervation potentials in the four extremities. No abnormalities were found on the electroencephalogram. The coefficient variation of the R–R intervals on electrocardiogram was normal.