FUNCTIONAL MAGNETIC RESONANCE IMAGING OF BRAIN MOTOR AREAS IN HEREDITARY SPASTIC PARAPARESIS PATIENTS

FUNKCIJSKO MAGNETNORESONANČNO SLIKANJE MOTORIČNIH PODROČIJ MOŽGANOV PRI BOLNIKIH S HEREDITARNO SPASTIČNO PARAPAREZO

Blaž Koritnik[1], Jernej Knific[2], Janez Zidar[1]

[1] Institute of Clinical Neurophysiology, Neurological Clinic, Clinical Center, Zaloška 7, 1525 Ljubljana, Slovenia
[2] Clinical Institute for Radiology, Clinical Center, Zaloška 7, 1525 Ljubljana, Slovenia

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Key words: *fMRI; voluntary movement; hereditary spastic paraparesis; motor cortex; cerebellum*

Abstract – Background. *Hereditary spastic paraparesis (HSP) is a heterogeneous group of disorders with corticospinal tract (CST) degeneration in which the main clinical feature is progressive bilateral lower limb spasticity. Functional imaging studies in patients with CST involvement have shown reorganization of motor cortex. Our study investigates functional adaptation of motor brain areas in HSP patients.*

Methods. *Nine HSP patients and 10 healthy subjects were studied. Functional magnetic resonance imaging (fMRI) was used to measure activation of cortical motor areas and cerebellum during finger tapping. Image analysis was performed using general linear model and regions-of-interest (ROI) based approach. Laterality indexes (LI) were calculated for cortical and cerebellar ROIs.*

Results. *Comparing patients and controls at the tapping rate of 1.8 Hz, there was higher fMRI activation in patients' ipsilateral lateral sensorimotor (iLSM) area and contralateral cerebellum (cCRB) compared to controls, while controls showed higher activation in cLSM and iCRB. LI was significantly lower in patients' LSM and CRB. Comparing patients and controls at 80% of their maximum tapping rates, the activation of cCRB was higher in patients, while cLSM and iCRB were higher in controls. LSM LI didn't differ significantly between the HSP and control groups, but the cerebellar LI was significantly lower in patients.*

Conclusions. *Our results suggest functional adaptation of the motor areas in HSP patients. The findings may reflect a combination of functional reorganization and compensatory brain activation at increased relative effort. Lower cLSM and iCRB activation in patients compared to controls might reflect the disorder of motor system in HSP.*

Ključne besede: *fMR; hoteno gibanje; hereditarna spastična parapareza; motorična skorja; mali možgani*

Izvleček – Izhodišča. *Hereditarna spastična parapareza (HSP) je heterogena skupina bolezni z degeneracijo kortikospinalnega trakta (KST). Glavna klinična značilnost je napredujoča obojestranska spastičnost spodnjih udov. S funkcijskimi slikovnimi metodami bolnikov s prizadetostjo KST so ugotovili reorganizacijo motorične možganske skorje. Z našo študijo smo preučevali funkcijsko prilagoditev motoričnih področij možganov pri bolnikih s HSP.*

Metode. *V študijo smo vključili devet bolnikov s HSP in deset zdravih preiskovancev. S funkcijskim magnetnoresonančnim slikanjem smo merili aktivacijo motoričnih področij možganske skorje in malih možganov med stikanjem prstov. Slike smo analizirali s pomočjo splošnega linearnega modela in z uporabo interesnih področij. Za interesna področja možganske skorje in malih možganov smo izračunali indekse lateralnosti (IL).*

Rezultati. *S primerjavo bolnikov in zdravih preiskovancev pri stikanju prstov s frekvenco 1,8 Hz smo pri bolnikih ugotovili večjo aktivacijo ipsilateralnega lateralnega sensorimotoričnega področja (iLSM) in kontralateralne polovice malih možganov (kMM), pri zdravih pa večjo aktivacijo kLSM in iMM. IL LSM in MM je bil pri bolnikih statistično pomembno nižji kot pri zdravih. S primerjavo bolnikov in zdravih preiskovancev pri stikanju prstov z 80% maksimalne frekvence smo pri bolnikih ugotovili večjo aktivacijo kMM, pri zdravih pa večjo aktivacijo kLSM in iMM. IL LSM se med skupinama nista statistično pomembno razlikovala, IL MM pa je bil manjši pri bolnikih.*

Zaključki. *Naši rezultati nakazujejo funkcijsko prilagoditev motoričnih področij možganov pri bolnikih s HSP. Možno je, da gre za kombinacijo funkcijske reorganizacije in nadomestne aktivacije zaradi večjega relativnega napora. Zmanjšana aktivacija kLSM in iMM pri bolnikih glede na zdrave preiskovance pa morda odraža okvaro motoričnega sistema pri HSP.*

Introduction

Hereditary spastic paraparesis (HSP) is a heterogeneous group of disorders in which the main clinical feature is progressive bilateral lower limb spasticity. Upper limb involvement is usually shown by mild hyperreflexia. HSP patients can be classified according to the mode of inheritance (autosomal dominant, autosomal recessive, X-linked), clinically (pure and complicated) and according to the specific genetic locus (SPastic parapleGia – SPG1 to SPG21). Complicated HSP has additional abnormalities such as seizures, dementia, cataracts, amyotrophy, extrapyramidal signs, cutaneous abnormalities, and peripheral neuropathy. The major neuropathological feature of pure HSP is axonal degeneration that is maximal in the terminal portions of corticospinal tracts (CST) and dorsal column pathways (»dying-back« type) (1–3).
Functional imaging studies in patients with CST involvement (HSP, amyotrophic lateral sclerosis, multiple sclerosis, spinal cord trauma) have shown reorganization of motor cortex (4–7). Our study investigates functional adaptation of motor brain areas in HSP patients.

Methods

Patients

Nine right-handed patients (from 8 different families; mean age 38 years, range 23–52, 4 males and 5 females) with pure or complicated HSP phenotype (Table 1) and ten right-handed healthy volunteers (mean age 33 years, range 23–51, 5 males and 5 females) were studied. Their lower and upper limb motor function was assessed by 9-hole peg test, maximum finger-tapping rate, and timed 5-meter walk. HSP inheritance was presumed autosomal dominant if one of the parents was affected as well, or autosomal recessive if another sibling was affected and the parents were healthy. There were no cases compatible with X-linked inheritance.

Functional imaging

Functional imaging was performed on a 1.5 T GE Horizon Signa LX scanner. Sixteen T2*-weighted EPI axial slices (TR 3 s, TE 40 ms, flip angle 90°, voxel size 3 × 3 × 7 mm) were acquired every 3 s. During fMRI scanning (two 1 min 36 s sessions; 24 s active blocks vs. 24 s rest) the subjects performed paced finger tapping (sequential 2^{nd}–5^{th} finger to thumb oppositions) with the right hand at a rate of 1.8 Hz, what was approximately 80 and 50% of the patients' and controls' maximum rate, respectively. Additionally, controls performed finger tapping at 80% of their individual maximum rate (on average 3.3 Hz) to match the task difficulty of patients.

Statistical analysis

Data was processed (spatial realignment, normalization, smoothing with a 12 mm FWHM Gaussian kernel) and analyzed using SPM2 software. Differences in contra- and ipsilateral lateral sensorimotor areas (cLSM and iLSM), medial motor area (MMA) and cerebellum (iCRB and cCRB) activation between patients and normal subjects were measured using regions-of-interest (ROIs) (Figure 1) and fixed-effects analysis

Table 1. *Patients' characteristics (MEP – motor evoked potentials, SEP – somatosensory evoked potentials, AR – autosomal recessive, AD – autosomal dominant, CC – corpus callosum, F – female, M – male, * – siblings).*

Patient	Sex	Age	Age at onset	HSP phenotype	Additional signs	Presumed inheritance	MEP	SEP	Brain MRI
1 AG	F	32	12	Pure		AR	Abnormal	N/A	Normal
2 JK	M	43	36	Pure		AD	N/A	N/A	Normal
3 LB*	M	23	17	Complicated	Learning difficulties, dysarthria	AR	N/A	N/A	CC atrophy, cortical and cerebellar atrophy
4 MB*	F	30	17	Complicated	Learning difficulties, dysarthria, amyotrophy	AR	Abnormal	N/A	CC atrophy, cortical and cerebellar atrophy
5 RK	M	27	15	Complicated	Nystagmus, peripheral neuropathy	AD	Abnormal	Abnormal	Mild cerebellar atrophy
6 DB	F	51	45	Pure		AD	N/A	N/A	CC atrophy, cortical and cerebellar atrophy, leucopathy
7 DG	F	35	29	Complicated	Learning difficulties, peripheral neuropathy	AR	Abnormal	Abnormal	Normal
8 AP	M	52	32	Pure		AD	Abnormal	Normal	Normal
9 EK	F	48	46	Pure		AR	Abnormal	Abnormal	Mild cortical and cerebellar atrophy

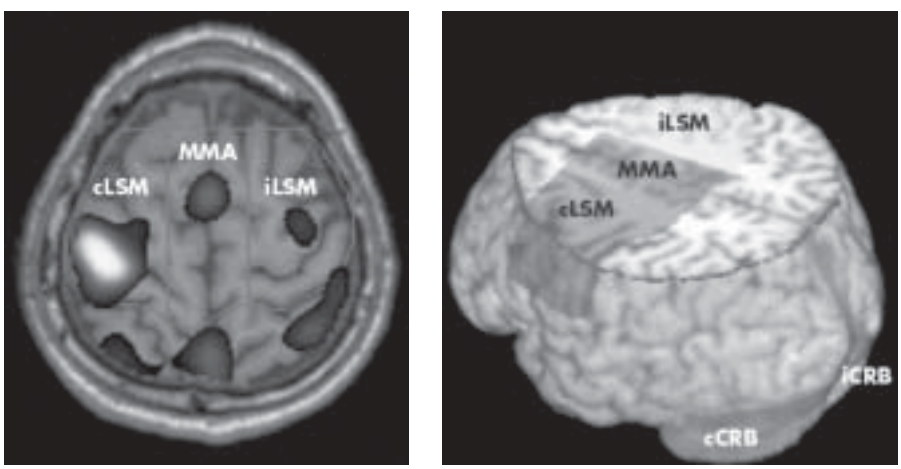

Figure 1. *Regions of interest were selected for each subject based on anatomical landmarks using MRIcro software. Contra- and ipsilateral sensorimotor areas (cLSM, iLSM) contained primary sensorimotor cortex and lateral premotor areas; medial motor area (MMA) contained supplementary and cingulate motor areas. The border between LSM and MMA was outlined post-hoc based on the activated clusters. Cerebellum was divided into the ipsilateral and contralateral half (iCRB, cCRB).*

($p < 0.05$ corrected). For each subject, laterality index (LI) was calculated for activated voxels in the predefined ROIs of the right (VR) and left (VL) cerebral and cerebellar hemispheres using the formula (VL-VR)/(VL+VR). The LI differences between groups were calculated using the nonparametric Mann-Whitney U test.

Results

The patient group functional capabilities (including maximum finger-tapping rate) were significantly inferior to those of the control group (Table 2). Comparing patients and controls at the same tapping rate of 1.8 Hz, the fixed-effects analysis showed higher fMRI activation in patients' iLSM and cCRB compared to controls, while controls showed higher activation in cLSM and iCRB (Figure 2). LI was significantly lower in patients' LSM and CRB, indicating a less lateralized brain activation (Figure 3).

Table 2. *Functional test results (mean values ± standard deviation).*

	Patients	Controls
9-hole peg test	25.8 ± 4.8 s	17.8 ± 2.5 s
Finger-tapping rate	2.1 ± 0.5 Hz	4.1 ± 0.8 Hz
5-meter walk	7.3 ± 3.4 s	2.5 ± 0.3 s

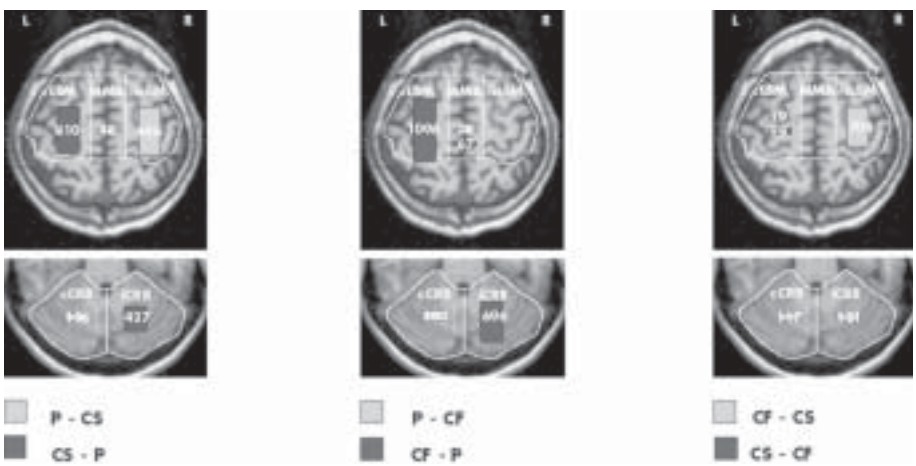

Figure 2. *Fixed-effects group analysis showing contrasts between patients, controls at fast rate and controls at slow rate. Number of activated voxels in predefined ROIs for each contrast is shown and represented by a rectangle (P – patients, CS – controls slow rare, CF – contrls fast rate).*

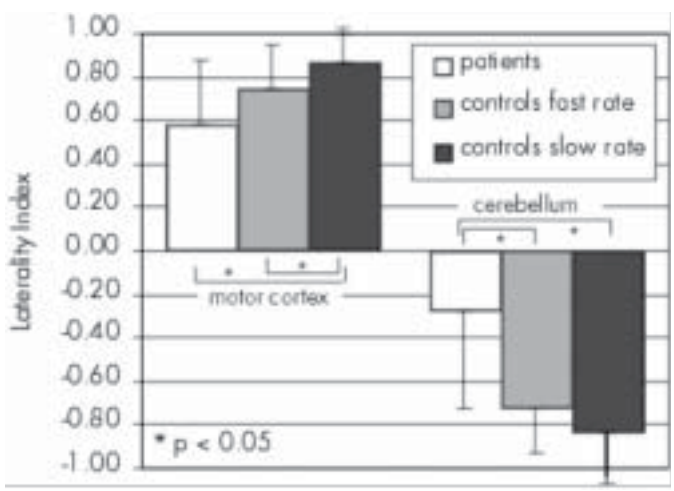

Figure 3. *Laterality indexes for motor cortex and cerebellum. Mean values are shown with standard deviations. Statistically significant differences ($p < 0.05$) are marked with an asterisk.*

Comparing faster and slower rates in controls, there was more iLSM and CRB activation at fast rate and more cLSM at slow rate. LSM and CRB LI were lower at faster rate. At same percentage of the corresponding maximum tapping rates, the activation of cCRB was higher in patients, while cLSM and iCRB were higher in controls. LSM LI didn't differ significantly between the HSP and control groups, but the cerebellar LI was significantly lower in patients.

Discussion

Higher activation of ipsilateral cortical motor areas and contralateral cerebellum in HSP patients suggests their functional adaptation during finger tapping. Modified motor cortex activation in HSP patients (a more widespread cortical cortical activation during shoulder and ankle movements compared to healthy controls) was also shown in a PET study (4). However, in our study healthy controls showed similar pattern of expanded motor cortex activation at increased effort. With the exception of contralateral cerebellar activity that could be attributed to reorganization, findings in HSP patients may therefore reflect mainly compensatory brain activation due to the increased relative effort. Controls showed more contralateral activation of the cortical motor areas and ipsilateral cerebellum at both slow and fast rates compared to the patients. This might be a direct consequence of the motor system pathology in HSP, not a functional adaptation. In another study, diffusion tensor imaging showed a bilateral reduced fractional anisotropy in the cerebral corticospinal tract in HSP patients (8). Our group of patients was defined clinically (and not genetically) and was heterogeneous. It was shown that clinical phenotypes and neurophysiological parameters differ between different types of HSP (9) and depend even on the type of mutation in the spastin gene (10). To better define the pattern of motor system reorganization, it would be worthwhile to study more homogeneous groups of HSP patients.

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