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Neurodegeneration in Friedreich's Ataxia Is Associated With a Mixed Activation Pattern of the Brain. A fMRI Study

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Abstract: Friedreich's ataxia (FRDA) is associated with a distributed pattern of neurodegeneration in the spinal cord and the brain secondary to selective neuronal loss. We used functional MR Imaging (fMRI) to explore brain activation in FRDA patients during two motor-sensory tasks of different complexity, i.e. continuous hand tapping and writing of "8" figure, with the right dominant hand and without visual feedback. Seventeen FRDA patients and two groups of age-matched healthy controls were recruited. Task execution was monitored and recorded using MR-compatible devices. Hand tapping was correctly performed by 11 (65%) patients and writing of the "8" by 7 (41%) patients. After correction for behavioral variables, FRDA patients showed in both tasks areas of significantly lower activation in the left primary sensory-motor cortex and right cerebellum. Also left thalamus and right dorsolateral prefrontal cortex showed hypo-activation during hand tapping. During writing of the "8" task FRDA patients showed areas of higher activation in the right parietal and precentral cortex, globus pallidus, and putamen. Activation of right parietal cortex, anterior cingulum, globus pallidus, and putamen during writing of the "8" increased with severity of the neurological deficit. In conclusion fMRI demonstrates in FRDA a mixed pattern constituted by areas of decreased activation and areas of increased activation. The decreased activation in the primary motor cortex and cerebellum presumably reflects a regional neuronal damage, the decreased activation of the left thalamus and pri-

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mary sensory cortex could be secondary to deafferentation phenomena, and the increased activation of right parietal cortex and striatum might have a possible compensatory significance. *Hum Brain Mapp 33:1780–1791, 2012*.

Key words: inherited ataxias; functional MRI; motor function

INTRODUCTION

Friedreich's ataxia (FRDA) is the most common recessively inherited ataxia, with a prevalence of around 2×10^{-5} in Caucasian [Pandolfo, 2009]. In about 95% of the cases, FRDA is due to a GAA repeat expansion in a gene located on chromosome 9q13 encoding a protein of unknown function named frataxin. The mutation implies loss of function of frataxin which is also reduced in amount [Pandolfo, 2009].

Neuropathological examination in FRDA demonstrates degeneration of multiple neuronal systems [Rewcastle, 1991] including both the primary and indirect (cerebellar) sensitive, the primary cortico-spinal and the visual systems. In particular there is a marked loss of large primary neurons in the dorsal root ganglia and of the neurons of the Clarke column in the spinal cord gray matter (GM) which is associated with loss of sensory fibers in peripheral nerves and degeneration of the gracilis and cuneatus and spinocerebellar white matter (WM) tracts in the spinal cord [Lowe et al., 1997; Rewcastle, 1991]. The corticospinal tract exhibits a dying back phenomenon, in that the degeneration is more prominent distally and in the spinal cord becomes less apparent as this tract is traced proximally through the brain stem. However most cases exhibit loss or shrinkage of the Betz and other pyramidal neurons of the motor cortex. Finally, retinal ganglion cells loss with optic atrophy and neuronal loss and gliosis of the lateral geniculate body are observed.

MRI shows a constellation of findings in FRDA including atrophy of the spinal cord and signal changes in the lateral and posterior columns of the spinal cord [Mascalchi et al., 1994], degeneration of the dentate nuclei [Waldvogel et al., 1999] and atrophy of the medulla and of the rostral vermis and infero-medial portion of the cerebellar hemispheres and atrophy and microstructural damage of several brain WM tracts including the inferior and superior cerebellar peduncles, the medial and lateral lemnisci, the corticospinal tracts and the optic tracts and radiations [Della Nave et al., 2008a,b; Fortuna et al., 2009; Pagani et al., 2010].

The main neurological features of FRDA include progressive cerebello-sensory ataxia of gait and limbs, peripheral sensory loss, loss of lower limb tendon reflexes, abnormal eye movements, and dysarthria with onset typically between 5 and 25 years of age [Klockgether, 2000; Pandolfo, 2009]. Clinical or subclinical visual or auditory compromise are frequently observed especially in the advanced phases of the disease [Fortuna et al., 2009; Klockgether, 2000; Pandolfo, 2009]. Although subtle abnormalities of executive functions were reported [Corben et al., 2006; De Nobrega et al., 2007], cognitive decline is not considered part of the clinical spectrum of the disease [Klockgether, 2000; Pandolfo, 2009].

Functional MR Imaging (fMRI) is contributing significant advances in the knowledge of the brain physiology in healthy subjects and physiopathology in patients with different neurological diseases. While several fMRI studies evaluated cerebellar activation during a number of motor-sensory and cognitive tasks in healthy subjects [Stoodley and Schmahmann, 2009] to date few fMRI studies in patients with ataxia have been published [Jayakumar et al., 2008; Mantovan et al., 2006]. In the only available fMRI study in FRDA [Mantovan et al., 2006] patients were reported to show very low blood oxygenation level dependent (BOLD) contrast with a heterogeneous pattern or lack of cerebral activation during a finger tapping task. No mention of possible cerebellar activation was made.

Two were the aims of this study: (1) to further investigate with fMRI brain activation in FRDA, and (2) to assess possible correlation of the functional changes with the severity of the clinical deficit. For such purposes we selected two tasks of different complexity, namely hand tapping and writing of an "8" [Saini et al., 2004], which basically explore motor features as force and coordination and for which we in-house developed low-cost MR-compatible devices enabling on-line control of the subject's performance [Diciotti et al., 2007, 2010]. The latter aspect is crucial for application of fMRI to patients who can present behavioral deficits as a consequence of their neurological disease [Price et al., 2006]. In healthy subjects the two tasks determine activation of primary sensorimotor cortex (SM1) and cerebellum [Diciotti et al., 2007, 2010] that is combined with activation of the parietal cortex in the case of the "8" writing task [Diciotti et al., 2010].

MATERIALS AND METHODS

Participants

We enrolled seventeen (eight men and nine women, mean age 33.2 ± 8.5 years) consecutive symptomatic right-handed patients with genetically proven FRDA. Molecular diagnostic methods for diagnosis of FRDA were previously reported [Bidichandani et al., 1998] and the cut-off number of abnormal triplet expansion qualifying for FRDA diagnosis was 100 GAA triplets on both alleles. The patient's score of clinical deficit was defined by the same neurologist at the time of the fMRI examination according to the inherited ataxia clinical rating scale (IACRS) which

TABLE I. Characteristics of the patient population and of the two subgroups that went into the final analyses

	Patients initially recruit	Patients who performed hand-tapping	Patients who performed "8" writing
Number	17	11	7
Gender M/F	8/9	5/6	4/3
Age (mean ± SD years)	33.2 ± 8.5	34.3 ± 8.5	38.6 ± 7.0
Disease duration (mean ± SD years)	14.7 ± 7.8	11.4 ± 4.3	12.6 ± 5.2
IACRS score (mean ± SD)	25.2 ± 8.3	21.6 ± 7.4	21.5 ± 7.1
Number of GAA triplets (mean ± SD)	538 ± 259	508 ± 236	463 ± 287

assesses both cerebellar and corticospinal deficits [Filla et al., 1990]. The mean IACRS score in the 17 FRDA patients was 25.2 ± 8.3. In particular, by dividing the scale scores in three categories of increasing neurological deficit, the patients were classified as with mild (three patients) (Score 0–15), moderate (eight patients) (Score 16–30) and severe (six patients) (Score 31–46) neurological deficit. The main clinical features of the initial patient population and of the two subgroups which underwent final fMRI analyses (see below) are summarized in Table I.

The fMRI results in FRDA were compared to those obtained in two groups of right-handed healthy volunteers constituted by 13 subjects (seven men and six women, mean age 31.9 ± 10.7 years) for hand tapping and nine subjects (six men and three women, mean age 34.4 ± 6.5 years) for writing of "8". They had no personal or familial history of neurological diseases and their neurological examination was normal. Definition of hand lateralization was accomplished using Edinburgh handedness scale [Oldfield, 1991].

MR Examination

Patients and controls were examined on a clinical 1.5 T system (Intera, Philips Medical System, Best, The Netherlands) with 33 mT/m gradients capability and a head coil with SENSE technology.

After scout, the examination protocol included a sagittal T1 weighted 3D T1-weighted turbo gradient echo sequence [repetition time (TR) = 25 ms, echo time (TE) = 4.6 ms, flip angle = 30°, field of view (FOV) = 256 mm, matrix size = 256 × 256, 160 contiguous slices, slice thickness = 1 mm] for voxel-based morphometry (VBM) and axial single-shot echo planar imaging sequence (TR = 9394 ms, TE = 89 ms, FOV = 256 mm, matrix size = 128 × 128, 50 slices, slice thickness = 3 mm, no gap, NEX = 3; diffusion sensitizing gradients applied along 15 non-collinear directions using b value of 0 (b0 image) and 1,000 s/mm^2) for diffusion tensor imaging (DTI) with TBSS. The results of VBM and DTI were reported elsewhere [Della Nave et al., 2008a,b; Pagani et al., 2010].

For the fMRI experiments we used a T2* weighted echo planar imaging sequence [repetition time (TR) = 3.0 s, echo time (TE) = 50 ms, flip angle = 90°, field of view 256 × 256 mm, matrix 128 × 128] exploiting the BOLD effect. Twenty-four axial 5 mm thick images were acquired parallel to the bi-commissural plane. Using a block design, where five periods of activation were alternated with seven periods of rest, each block lasting 15 s, the total acquisition time for each task was about 3 min.

For both the hand tapping and writing of an "8" task the subject was requested to perform the task continuously at a self-paced frequency without visual feedback. Also force in the case of hand-tapping and size of the figure in the case of writing of "8" were freely chosen by the subject but he/she was requested to maintain the three variables as constant as possible during the experiment. After checking the capability of the subject to perform the tasks and a brief training outside the magnet, the subjects were requested to perform the tasks within the magnet with the monitoring devices on before fMRI acquisitions.

The devices used in the study are extensively described elsewhere [Diciotti et al., 2007, 2010] and enable to visualize in real time the subject's behavior and to measure off-line the frequency and the force exerted in the case of hand tapping and the frequency and size of the "8" figures in the case of the writing of the "8".

Briefly, for the hand tapping task we developed a device composed of an air-filled rubber bulb commonly adopted in sphygmomanometers, a plastic tube, a pressure transducer, a signal conditioning electronics, a data acquisition device, and a personal computer (PC). The bulb was fixed on a cotton glove with a velcro strip. The glove allows the subject not to grasp the rubber bulb in the palm of the hand and to perform a natural movement of pressing the rubber bulb with the last four fingers of the hand. The device measures the force and frequency exerted by the subject in pressing an air- filled rubber bulb with the last four fingers.

For the writing of the "8" task we developed a device composed of a light-emitting pen connected to a light beam generator placed outside the MR room by an optical fiber, a partially transparent tracing plane fixed to the top of a cylindrical-shaped equipment support which at its base has a camera. The tracing plane is tilted about 30–40° on the horizontal plane to allow a comfortable position for the subject's wrist during hand tracing. The light beam arising from the tip of the pen forms a light spot, which filters inside the cylindrical support and describes the pen trajectories executed by the subject. These are recorded by the camera fixed on the bottom of the cylindrical support. The camera is connected to a PC, placed in an adjacent room, by a USB cable equipped with an electromagnetic interference filter. Pen trajectories are extracted by a blob detection algorithm through Laplacian of Gaussian filtering applied to the camera recordings.

Hand-tapping was always executed first in the case the subject could perform both tasks. The tasks were

externally paced using spoken words "go" and "stop" to initiate and terminate active blocks and the subjects were instructed to keep their eyes closed during fMRI acquisitions.

3D T1-weighted turbo gradient echo scans were used to facilitate anatomical localization of the functional data after registration.

Behavioral Analysis

Hand tapping task

In real-time, each force signal was inspected for possible gross errors including hand-tapping interruption during active phases or hand-tapping during resting phases. The force signals were recorded by a PC and processed by software analysis in order to extract quantitative parameters which describe the motor performance [Diciotti et al., 2007]. To this end, the task was analyzed in terms of strength and frequency of flexion-extension of the last four fingers of the hand. For each parameter, the mean value and the coefficient of variation (CV) throughout the task were computed. For each trial, the force signal was also examined to determine a possible fatigue phenomena, defined as a reduction of 40% or more of the force exerted to press the bulb within each active block or between active blocks [Liu et al., 2005].

Writing of the "8" task

The recordings of "8" writing task were visually inspected on line for gross artifacts for detection of possible gross errors including the writing of a figure different from an "8", any writing interruption during active phases or any writing during resting phases. For each task recording the mean frequency and the mean size of the "8" figures, the coefficient of variation of the frequency and of the size were computed [Diciotti et al., 2010].

The Mann-Whitney test was utilized to evaluate possible differences in motor performance parameters between FRDA patients and controls with a significance threshold of $P = 0.05$.

Finally, the IACRS scores of patients who successfully performed the task were compared with those who failed the task by using a Mann-Whitney test with $P < 0.05$.

fMRI Data Analysis

Functional data related to the two motor tasks were analyzed according to a previously reported procedure [Diciotti et al., 2010] using FSL 4.0 software (Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) software library, available at http://www.fmrib.ox.ac.uk/fsl). The first five scans of each run were discarded from analysis in order to avoid T1-related relaxation effects. The following prestatistics processing were applied to the remaining 55 scans: motion correction using MCFLIRT [Jenkinson et al., 2002], slice-timing correction (interleaved acquisition), nonbrain removal using BET [Smith, 2002], spatial smoothing using a 8 mm FWHM Gaussian kernel, high-pass temporal filtering (cut-off point 30 s), grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor.

Preliminarily we assessed in all subjects possible occurrence of head motion unrelated or related to the task execution. In particular the subjects were excluded from further analyses if absolute head displacement was greater than 3 mm in more than five acquisition volumes or if the correlation between movement parameters and task regressors was greater than 0.5 [Gountouna et al., 2010].

Registration of the EPI functional images to the individual high resolution T1-weighted image and standard space [Talairach and Tournoux, 1988] was carried out using an affine transformation with 12 degrees of freedom [Jenkinson and Smith, 2001].

The FMRIB's improved linear model [Woolrich et al., 2001] was adopted for statistical analysis in order to determine the activation maps of signal changes between active versus rest periods for acquisitions of both tasks. First-level statistical analysis was performed by General Linear Model (GLM) approach. The expected BOLD responses were obtained by convolving the original predictors waveforms with a gamma-form haemodynamic response function. The design matrix of GLM also included the temporal derivative of the blurred original waveform, which is equivalent to shifting the waveform slightly in time, in order to achieve a slightly better fit to the data. For normal first-level time series analyses, we used prewhitening to make the statistics valid and maximally efficient. Single-subject (first-level) cluster analysis was performed on voxels having Z (Gaussianised T) > 2.3 and a (cluster-based corrected) significance threshold of $P = 0.001$ [Worsley, 2001].

For higher-level analyses (within-group and between-group) we employed FMRIB's Local Analysis of Mixed Effects (FLAME) using first-level COPE (contrast of parameter estimates) images as input.

Within-group analysis was carried out using one-sample *t*-test to assess the differences between the active and passive blocks and a fixed effects model by forcing the random effects variance to zero in FLAME [Beckmann et al., 2003; Woolrich et al., 2004; Woolrich, 2008]. Within-group analysis was separately carried out for FRDA patients and controls for both tasks. Since some behavioral features as the frequency of both tasks and the force of hand tapping and size of the "8" figure can modulate brain activation [Dai et al., 2001; Deiber et al., 1999; Diciotti et al., 2010; Schlaug et al., 1996] we inserted the frequency, the force, the frequency CV and the force CV, for the hand tapping task, and the frequency, the size of the "8" figures, the frequency CV and the size CV, for the writing of the "8"task, as covariate variables within the GLM matrix. The *Z*-statistical maps derived from the within-group analysis underwent a cluster thresholding with a *Z* threshold of 3.8 and a cluster *P* threshold of 0.05 [Worsley, 2001].

TABLE II. Behavioral parameters showing the motor performance of FRDA patients and controls while performing hand-tapping and writing of "8" figures

	Hand-tapping				"8" writing			
	Frequency (Hz)	Frequency CV (%)	Force (N)	Force CV (%)	Frequency (Hz)	Frequency CV (%)	Size (mm^2)	Size CV (%)
FRDA patients	0.61 ± 0.24 (0.22, 1.06)	9.9 ± 2.8 (5.7, 13.9)	25.3 ± 3.2* (20.6, 30.4)	5.1 ± 2.5 (2.6, 10.9)	0.51 ± 0.11 (0.4, 0.66)	12.2 ± 4.3 (6.3, 20)	495.8 ± 424.9 (75.2, 1236.6)	40.4 ± 18 (19.9, 75.1)
Controls	0.56 ± 0.20 (0.37, 1.05)	9.4 ± 2.0 (5.5, 13.4)	29.2 ± 3.1* (23.2, 34.6)	4.0 ± 2.2 (1.6, 8.3)	0.70 ± 0.25 (0.35, 1.09)	9.9 ± 2.9 (5.4, 14.6)	668.2 ± 336.1 (237.8, 1367.4)	24.9 ± 10.5 (14.3, 46.5)

Mean ± standard deviation (minimum value, maximum value) data are reported. CV, coefficient of variation.
*$P = 0.01$, Mann-Whitney test.

To assess possible differences in the BOLD activation pattern between FRDA patients and controls a between-group analysis was carried out using unpaired *t*-test and a fixed effects model, by forcing the random effects variance to zero in FLAME [Beckmann et al., 2003; Woolrich et al., 2004; Woolrich, 2008]. *Z* (Gaussianized *T/F*) statistic images were thresholded using clusters determined by $Z > 3.8$ and a (corrected) cluster significance threshold of $P = 0.05$ [Worsley, 2001].

Finally, to evaluate a possible relationship between changes of cortical activation and disease severity, a second within-group analysis was carried out in the FRDA patient group only using one-sample *t*-test and FMRIB's Local Analysis of Mixed Effects [Beckmann et al., 2003; Woolrich et al., 2004] with IACRS scores as further explanatory variables. *Z* (Gaussianized *T/F*) statistic images related to IACRS score explanatory variable were thresholded using clusters determined by $Z > 3.8$ and a (corrected) cluster significance threshold of $P = 0.05$ [Worsley, 2001].

To achieve a more accurate spatial localization of the significant clusters of activation identified at the within and between-group analyses, we overlaid the corresponding activation maps with the Automated Anatomical Labelling (AAL) map using a custom made software and computed the size of each activated anatomical area and relative maximum *Z* score [Tzourio-Mazoyer et al., 2002]. Moreover the Schmahmann et al. [1999] MRI atlas of the human cerebellum was used as an anatomical reference to assess the exact localization of the activated clusters in the cerebellum.

RESULTS

Behavioral

Hand tapping

Sixteen (94%) FRDA patients (eight men and eight women) were able to correctly perform the task within the magnet (Table I). One patient (with IACRS score of 35) was not able to correctly perform the task outside the magnet. Five of the 16 patients were excluded from further fMRI analyses because of head motion unrelated (two patients) or in phase with the task (three patients). Differences for gender (χ^2 test) and age (Mann-Whitney test) between the remaining 11 (65%) FRDA patients who successfully performed the hand tapping task and the healthy controls were not significant ($P > 0.05$).

Table II details the features of the hand tapping task execution as measured by the device. Of all behavioral parameters, only the force was significantly different (lower) in FRDA patients as compared to controls.

Writing of the "8" figure

Eleven (65%) FRDA patients correctly performed the task within the magnet (Table I). One patient was not able to perform the task outside the magnet, while five patients were not able to perform the task with the device inside the MR gantry in the trial before fMRI acquisition. The IACRS scores were significantly lower ($P = 0.01$) in the 11 successful FRDA patients (21.6 ± 7.4) as compared to the six who failed (31.8 ± 5.0). Four of the 11 patients were excluded from further fMRI analyses because of head motion in phase with the task. Differences for gender (χ^2 test) and age (Mann-Whitney test) between the 7 (41%) remaining FRDA patients who successfully performed the task and controls were not significant ($P > 0.05$).

Table II details the features of the writing of the "8" task execution as measured by the device. All behavioral parameters were not significantly different between FRDA patients and controls.

Functional MRI

Hand tapping

Within-group analysis showed that during hand tapping both healthy controls and FRDA patients showed bilateral activation in SM1 (more pronounced in the left), the supplementary motor area (SMA), the insula and the

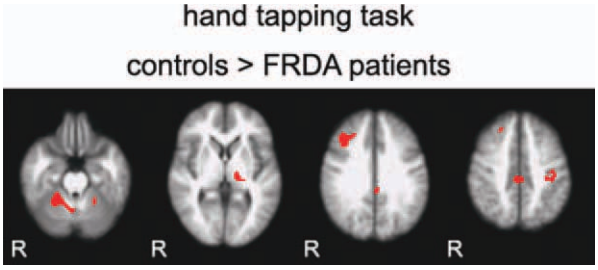

Figure 1.
Selection of the activation map during the hand tapping task. The between group analysis shows clusters of significantly ($Z > 3.8$, $P \leq 0.05$ corrected) higher activation in healthy subjects as compared with FRDA patients during hand tapping task. They include the left SM1 cortex, the SMA, bilaterally, the right frontal cortex, left thalamus and right cerebellar hemisphere (V and VI lobules), the vermis (right portion of the V lobule) and left cerebellar hemisphere (border zone between left V and VI lobules).

cerebellar hemispheres. In the cerebellum activation involved the V, VI and VIIIA and VIIIB lobules bilaterally but more pronouncedly in the right side.

The results of the between-group analysis are shown in Figure 1 and reported in Table III.

As compared with the healthy controls, patients with FRDA exhibited areas of significantly lower activation in the left SM1, the SMA bilaterally and the right mid frontal gyrus. Additional clusters of reduced activation were also detected in the left thalamus (nucleus ventralis anterior and nucleus ventralis lateralis) and in the cerebellar hemispheres, in the right V and VI lobule and at the border zone between left V and VI lobules, and in the vermis in the right portion of the V lobule.

FRDA patients did not show areas of higher activation with respect to controls.

No correlation was found between brain activation and IARCS score.

"8" figure writing

Within-group analysis showed that during writing of the "8", both FRDA patients and healthy controls showed activation in the left SM1 cortex, the right premotor frontal and parietal cortex, the right globus pallidus and putamen and the cerebellar hemispheres and vermis. In the right cerebellar hemisphere activation was more marked and involved the V, VI and Crus I and VIIIA and VIIIB lobules. In the left cerebellar hemisphere activation involved the V, VI and VIIIA and VIIIB lobules. An additional cluster was present in the lobule IV and V of the vermis in the right side.

The results of the between-group analysis are shown in Figure 2 and reported in Table IV.

As compared with the healthy controls, patients with FRDA exhibited areas of significantly lower activation in the left SM1 and right cerebellar hemisphere in the right VI lobule extending to the right Crus I (Fig. 2A). Conversely, FRDA patients showed clusters of significant higher activation in the right precentral and parietal cortex and the right globus pallidus and putamen (Fig. 2B).

The correlation analysis revealed that in FRDA patients activation of the right globus pallidus and putamen, anterior cingulus, and parietal cortex increased with IACRS score (Fig. 2C; Table V).

DISCUSSION

Principal Findings of This Study

The present investigation indicates that a proportion of patients with FRDA and overt clinical deficit are able to correctly perform motor tasks of varying complexity during fMRI acquisition. After correction for behavioral variables which can influence brain activation, multiple changes in terms of decreased or increased regional activations implying involvement of different systems are demonstrated by fMRI in FRDA patients as compared to

TABLE III. Results of the between group analysis during right hand tapping task

Anatomical area	Cluster size (mm^3)	MNI coordinates of voxel with maximum Z score (mm)		
		x	*y*	*z*
Controls > FRDA				
Left supplementary motor area	271	−4	−13	67
Right supplementary motor area	58	1	−3	65
Left precentral gyrus	658	−35	−27	55
Left postcentral gyrus	3,525	−42	−19	49
Right mid frontal gyrus	2,003	38	27	33
Left thalamus (nucleus ventralis anterior, nucleus ventralis lateralis)	772	−16	−21	7
Right cerebellar hemisphere (lobules V and VI)	3,912	22	−43	−21
Vermis (right portion of lobule V)	206	6	−57	−21
Left cerebellar hemisphere (lobules V and VI)	1.241	−32	−51	−33

MNI, Montreal Neurological Institute.

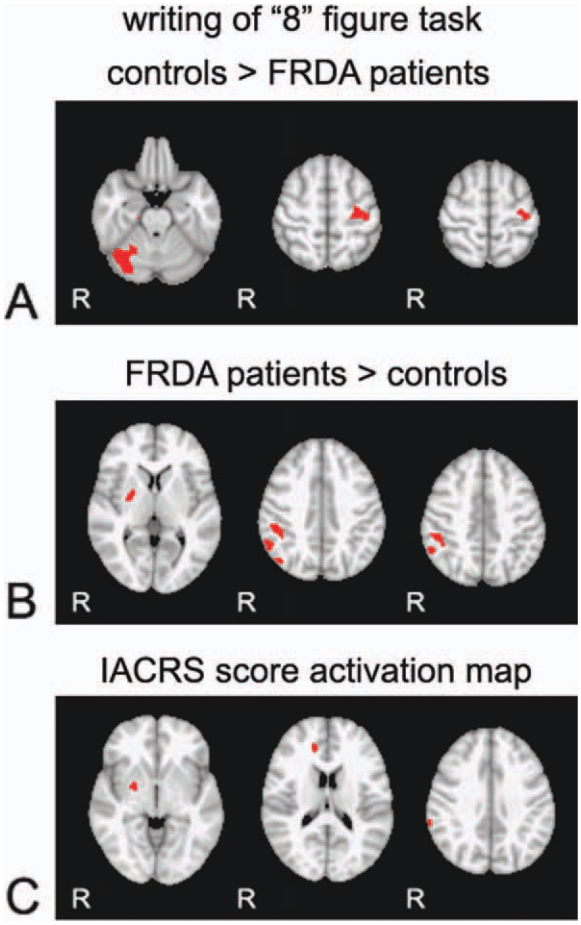

Figure 2.

A–C: Selections of the activation maps during the writing of "8" task. Maps of between group analysis show clusters of significantly ($Z > 3.8$, $P \leq 0.05$ corrected) higher activation in healthy subjects as compared with FRDA patients, including left SM1 and right cerebellar hemisphere (VI lobule extending to the Crus I) (A), and higher activation in FRDA patients as compared with healthy subjects, including right precentral and parietal cortex, globus pallidus and putamen (B). **C**: Map of within group analysis in the FRDA patients obtained by introducing IACRS score as covariate in the model demonstrates that activation in right globus pallidus and adjacent putamen, anterior cingulus and parietal cortex increases with IACRS score ($Z > 3.8$, $P \leq 0.05$ corrected).

age-matched healthy subjects. These include: (1) decreased activation in the primary motor cortex and cerebellum on both tasks that presumably reflects the regionally selective neuronal damage which is demonstrated by the neuropathological examination; (2) decreased activation of the primary sensory cortex on both tasks and of the thalamus on hand tapping task that could reflect deafferentation phenomena; (3) increased activation of right striatum and parietal cortex on writing of the "8" that is correlated with the severity of clinical deficit and might have a possible compensatory significance.

TABLE IV. Results of the between group analysis during "8" figure writing task

Anatomical area	Cluster size (mm^3)	MNI coordinates of voxel with maximum Z score (mm)		
		x	*y*	*z*
Controls > FRDA				
Left precentral gyrus	1773	−36	−21	57
Left postcentral gyrus	470	−36	−21	55
Right cerebellar hemisphere (Lobule VI and Crus I)	4301	30	−73	−23
FRDA > Controls				
Right precentral gyrus	236	34	−9	53
Right inferior parietal gyrus	759	56	−53	41
Right putamen	676	26	−3	5
Right globus pallidus	122	24	−1	5

MNI, Montreal Neurological Institute.

Task Performance

The fundamental assumption for application of fMRI to investigation of brain physiopathology in patients with neurological disorders requires that patients perform the task in the same way as healthy subjects do [Price et al., 2006]. If this is not the case, measurements of different behavior can be incorporated in the statistical model as covariates.

Besides the severe sensitive compromise which hinders utilization of sensitive stimuli for fMRI, patients with FRDA suffer from a variable motor dysfunction. In fact the spinocerebellar and cerebellar dysfunction typically determines limb ataxia and prolonged movement times [Corben et al., 2009] and the corticospinal dysfunction is responsible for decreased force. In this investigation we chose two motor tasks of different complexity [Diciotti et al., 2007, 2010; Saini

TABLE V. Results of the within group analysis in FRDA patients during right hand tapping task using IACRS score as explanatory variable

Anatomical area	Cluster size (mm^3)	MNI coordinates of voxel with maximum Z score (mm)		
		x	*y*	*z*
Right inferior parietal gyrus	64	56	−61	41
Right anterior cingulum	167	14	41	19
Right globus pallidus	186	24	−1	−3
Right putamen	136	20	19	−9

MNI, Montreal Neurological Institute.

et al., 2004]. However, both tasks also involve sensitive components which are related to the perception (mediated by the glove) of the rubber bulb in the case of hand tapping and of the pen in the case of "8" writing. Admittedly the latter aspects, namely the degree of perception by the patients, which could in principle determine some independent brain activation or modulate those we observed, were not evaluated in the present investigation.

During both tasks and notably the writing of the "8" we did not allow visual control of the task by the subject. This was justified by both the easier set-up and by the observation that oculomotor activity can significantly interfere with cerebellar activation [Glickstein et al., 2009].

In this study all behavioral features measured in the FRDA patients by force of hand tapping were similar to those of the healthy control subjects. This notwithstanding force of hand tapping and the other behavioral variables potentially modulating brain activation were inserted as covariates in the statistical models [Diciotti et al., 2010].

Methodological Considerations

In the only available fMRI study in FRDA a visual monitoring of the finger tapping task was carried out [Mantovan et al., 2006]. However, accurate monitoring of task performance is required to avoid major biases in fMRI studies of patients with neurological diseases [Price et al., 2006]. Prior studies in healthy subjects have demonstrated that brain activations, in particular of the SM1 and cerebellum, associated with motor tasks are modulated by behavioral parameters such as force, frequency, and amplitude of the movement [Dai et al., 2001; Deiber et al., 1999; Diciotti et al., 2010; Lutz et al., 2005; Schlaug et al., 1996]. As a consequence, the discrepancy between patients and controls observed in unmonitored tasks could be simply related to a discrepancy in task performance. To avoid such bias, we adopted MR-compatible instruments to strictly monitor the task of both patients and controls inside the magnet [Diciotti et al., 2007, 2010] and included the behavioral parameters in the model of statistical analysis as confounding variables.

Notwithstanding exclusion of several patients due to incapacity to perform the task, incorrect task execution within the magnet or movement artifacts, our study demonstrates that patients with FRDA and substantial clinical deficit can correctly perform motor tasks during fMRI acquisitions.

In particular, it confirms that the device for hand tapping monitoring can be successfully applied to investigation with fMRI of symptomatic patients with neurological diseases [Tessa et al., 2010].

Moreover our study confirms that selection of a critically difficult task, in this study the continuous "writing of the "8", is crucial to unveil activation in cortical and subcortical areas of possibly compensatory significance put in place by the diseased brain to maintain the functional level necessary to correctly execute the task itself [Wolf et al., 2007].

An additional special problem in application of fMRI to degenerative diseases of the CNS is the possible coexistence of significant regional brain atrophy which may act as a confounding implying a decreased BOLD effect unrelated to decreased activation [Gavazzi et al., 2007; Wolf et al., 2007]. All the FRDA patients in the present investigation took part in a prior VBM study which revealed regional atrophy in dorsal medulla, infero-medial portions of the cerebellar hemispheres, the rostral vermis and in the dentate region but no volume loss in the cerebral hemispheres [Della Nave et al., 2008a]. Apart from atrophy being a possible contribution to the decreased activation observed in the cerebellum, regional atrophy can reasonably be excluded as a major determinant of the decreased activation we found in other regions, notably in the cerebral hemispheres.

Regional Changes in Brain Activation

SM1

The decreased activation of the primary motor cortex observed in FRDA patients as compared with healthy controls during execution of both hand tapping and writing "8" tasks presumably reflects the neuronal damage secondary to frataxin deficiency demonstrated in this region by the neuropathological examination [Rewcastle, 1991]. Since during both tasks the hypoactive area comprised the primary sensory cortex where no change is demonstrated by the neuropathological examination, it is possible that such an hypoactivation might reflect deafferentation effects (see below).

Cerebellum

The predominant activation of the lobules V and VI of the right cerebellar hemisphere with a second cluster in the VIII lobule of the same hemisphere in our healthy subjects and FRDA patients during both hand tapping and writing of the "8" tasks is in line with prior fMRI studies using finger tapping, hand tapping or flexo-extension movements in healthy subjects [Stoodley and Schmahmann, 2009].

No cerebellar activation was mentioned in FRDA patients during a finger tapping task in a prior study [Mantovan et al., 2006]. The relative preservation of cerebellar activation we found is in line with the paucity of the MRI atrophic changes in the cerebellum known in FRDA [Rewcastle, 1991; Lowe et al., 1997] and documented by VBM in this sample of patients [Della Nave et al., 2008a]. Despite this, as expected, cerebellar activation was significantly decreased during both tasks in FRDA patients as compared with healthy controls. Although the cerebellar hypoactivation presumably reflects the regional neuronal damage secondary to frataxin

deficiency demonstrated in this region by the neuropathological examination [Lowe et al., 1997; Rewcastle, 1991] a possible contribute of deafferentation phenomena cannot be excluded (see below).

Thalamus

In our study FRDA patients showed during hand tapping significant hypoactivation of the left thalamus (nucleus ventralis anterior and nucleus ventralis lateralis) as compared with healthy controls.

Thalamus has no motor function, but has a fundamental role in conveying the mainly crossed sensitive information coming from the spinal cord and brainstem to the cerebral cortex. In particular the thalamus is a fundamental relay station of both the primary and the indirect (cerebellar) sensitive pathways which are dysfunctional in FRDA to the frontal motor cortex. In fact the spinal ganglion cell damage associated with atrophy and structural changes of the gracilis and cuneatus WM tracts is likely to determine transneuronal damage of the gracilis and cuneatus nuclei in the brainstem and of the medial lemnisci which represent their crossed projections to the thalami. On the other hand the damage of the Clarke column in the spinal cord and of the posterior spinocerebellar tracts of the spinal cord along with the cerebellar cortical damage and the severe neuronal loss and gliosis of the dentate nucleus imply a substantial damage of the dentate-thalamic fibers contained in the superior cerebellar peduncles and of the dentate-rubro-thalamic fibers [Testut and Latarjet, 1971].

Given the substantial preservation of the thalamus in FRDA demonstrated by the neuropathological studies [Oppenheimer, 1984; Rewcastle, 1991], we submit that the decreased thalamic activation observed in our FRDA patients during hand tapping is likely to reflect deafferentation phenomena secondary to the damage of the primary and cerebellar sensitive pathways. The possibility that a distributed pattern of WM tract atrophy and microstructural damage is responsible for regionally specific decreased BOLD contrast in the cortical and subcortical GM has already been hypothesized to explain the decreased functional connettivity demonstrated by resting state fMRI in presymptomatic and symptomatic carriers of Huntington's disease [Thirudavy et al., 2007; Wolf et al., 2008].

SMA

During hand tapping FRDA patients showed hypoactivation of the SMA bilaterally as compared with healthy controls.

The main role of SMA is in the initiation of movement and in the ability to prepare and perform alternative movements [Laplane et al., 1977]. Hypoactivation of SMA reversed by dopamine administration is observed in patients with Parkinson's disease during motor tasks of different complexity [Buhmann et al., 2003; Haslinger et al., 2001] and is thought to reflect the functional connection with the basal ganglia and hence the dysfunction of the basal-ganglia-thalamocortical circuit in Parkinson's disease. Although based on the evidence of pallidal damage Oppenheimer [1994] documented in a series of 15 FRDA patients a similar mechanism could be operating also in FRDA, we submit an alternative explanation.

Namely, decreased SMA activation in FRDA during hand tapping might reflect the fact that since FRDA patients exhibit a deficit of force they would pay increased attention to correctly perform the alternate movement of hand tapping and at least two studies demonstrated that decreased SMA activation during motor tasks in Parkinson's disease patients was due to increased attention [Rowe et al., 2002; Wu and Hallet, 2005]. Notably this mechanism is not operating during "8" writing task which the patients performed without any significant difference as compared with the controls.

Right middle frontal gyrus

During hand tapping FRDA patients showed significantly lower activation of the right middle frontal gyrus as compared to controls. This region corresponds to the dorsolateral prefrontal cortex (DLPFC) which plays a role in the executive-control adjustment and in dynamic tuning of executive control [Mansouri et al., 2009]. Interestingly, a selective deficit in phonemic and action fluency performance [De Nobrega et al., 2007] as well as in motor reprogramming [Corben et al., 2006] was reported in FRDA patients. These subtle cognitive changes suggest a prefrontal dysfunction in FRDA which was thought secondary to a regional cerebral pathology or to affection of the cerebello-thalamo-cortical pathway originating in the dentate nucleus and projecting to the DLPFC [Allen et al., 2005; Middleton and Strick, 1997; Schmahmann and Pandya, 1995]. On the basis of the lack of neuropathological evidence of cerebral cortical damage outside the M1 in FRDA [Rewcastle, 1997] we submit that the decreased activation of the right DLPFC in our FRDA patients during hand tapping which mirrors the executive dysfunction reported above reflects a deafferentation phenomena. In our opinion failure of a more demanding task as writing of the "8" in revealing a similar feature might be due to the smaller number of FRDA patients who successfully performed the task in our study weakening the statistical power of the between group analysis.

Striatum

During "8" figure writing FRDA patients showed hyperactivation in the right pallidum and putamen which increased parallel to the clinical deficit measured by the IACRS.

Studies in primates and rodents have revealed that the deep nuclei of the cerebellum and the putamen or globus pallidus are interconnected directly or through the thalamus, the zona incerta, the fields of Forel and red nucleus

[Hoshi et al., 2005; Pong et al., 2007]. Although Oppenheimer [1984] reported neuronal loss in the globus pallidus, the hyperactivation observed within the right striatum during writing of the "8" suggests an intriguing compensatory mechanism.

Indeed, as known from previous physiological and neuroimaging studies [Haber and Calzavara, 2009; Jueptner and Weiller, 1998; Kopell et al., 2006; Middleton and Strick, 2000], cerebellum and basal ganglia play a different role in the control of movements. The neocerebellum (cerebellar nuclei and hemispheres) is more engaged in monitoring and optimizing movements using proprioceptive feedback, while basal ganglia are not involved in the processing of sensory information [Jueptner and Weiller, 1998]. Since in FRDA both the spinocerebellar proprioceptive projections and the neocerebellum are impaired, we may hypothesize that the increased basal ganglia activation might help to support the motion control function.

The increased activation of right striatum of possible compensatory significance observed during a more demanding task in our FRDA patients confirms the anatomical and functional integration between the cerebellum and the basal ganglia.

Parietal and cingulate cortex

During "8" figure writing FRDA patients showed hyperactivation in the right inferior parietal cortex. Moreveor, during the same task, activation of the right inferior parietal and anterior cingulate cortex significantly increased with clinical deficit as measured by the IACRS score.

Recent imaging and lesion studies have revealed that inferior parietal regions have nonspatial functions, such as in sustaining attention, detecting salient events embedded in a sequence of events and controlling attention over time [Husain and Nachev, 2007].

On the other hand the primate anterior cingulate cortex plays critical roles in performing appropriate actions with attention, especially in the case of complex sequential tasks [Playford et al., 1992] as continuous writing of the "8", and in checking the performance to acquire rewards efficiently [Isomura and Takada, 2004].

We submit that the greater complexity of "8" writing as compared to hand tapping was successful in unveiling compensatory mechanisms in FRDA patients who recruited more vigorously the right inferior parietal and anterior cingulated cortex to perform sequential movements successfully.

Limitations of the Present Study

We recognize two limitations of our study. First, by using active motor tasks for fMRI we de facto excluded from analysis FRDA patients with greater neurological deficits. This may cast doubt on the general applicability of these methods to patients with neurodegenerative diseases of the CNS implying compromised motor function and on the potential of using these tasks for monitoring disease progression. Passive motor tasks or "resting state" fMRI may be more useful for the latter purpose but they were not used in the present investigation.

Second, the experimental design of the study did not allow to clearly distinguish between effects of regional neuronal loss, altered sensory feedback and possible compensatory mechanisms. Further fMRI investigations using sensory tasks combined with passive and active motor tasks might clarify this issue.

CONCLUSIONS

The mixed pattern constituted by areas of decreased activation and area of increased activation revealed by fMRI in our symptomatic patients with FRDA is in line with the fMRI results obtained using motor tasks in other neurodegenerative movement disorders, such as amyotrophic lateral sclerosis, Huntington's disease and Parkinson's disease [Gavazzi et al., 2007; Kloppel et al., 2009; Stanton et al., 2006; Tessa et al., 2010], all characterized by a distributed pattern of neuronal dysfunction and loss. The mixed pattern presumably results from a combination of regional primary neurodegeneration, deafferentation, and compensatory mechanisms. The importance of the primarily neuronal damage as underlying pathology responsible of such a mixed pattern in FRDA is suggested by the observation of a normal brain activation pattern at fMRI during flexion-extension of the hand reported in a patient with subacute combined degeneration [Filippi et al., 2003]. Intriguingly, this is a condition due to Vitamin B12 deficiency which is characterized pathologically by a potentially reversible demyelination with a distribution in the posterior and lateral columns of the spinal cord and in the brain primary motor cortex and cortico-spinal tracts which is similar to that of FRDA.

Exploration with fMRI of degenerative diseases of the CNS is of theoretical and potentially practical importance. In fact it enables assessment of the pathophysiological changes characteristic of each disease. Moreover, in view of new therapeutic measurements aimed to halt or slow progression of neurodegeneration [Taroni and Di Donato, 2004], fMRI should be evaluated as a potential surrogate marker in future clinical trials of FRDA. This possibility is justified by the low sensitivity of clinical measurements to disease progression [Friedman et al., 2010].

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