



Longitudinal Increases in Cerebral Brain Activation During Working Memory Performance in Friedreich Ataxia: 24-Month Data from IMAGE-FRDA

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Published online: 2 January 2020

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Abstract

Friedreich ataxia (FRDA) has been associated with functional abnormalities in cerebral and cerebellar networks, particularly in the ventral attention network. However, how functional alterations change with disease progression remains largely unknown. Longitudinal changes in brain activation, associated with working memory performance (N-back task), and grey matter volume were assessed over 24 months in 21 individuals with FRDA and 28 healthy controls using functional and structural magnetic resonance imaging, respectively. Participants also completed a neurocognitive battery assessing working memory (digit span), executive function (Stroop, Haylings), and set-shifting (Trail Making Test). Individuals with FRDA displayed significantly increased brain activation over 24 months in ventral attention brain regions, including bilateral insula and inferior frontal gyrus (pars triangularis and pars opercularis), compared with controls, but there was no difference in working memory (N-back) performance between groups. Moreover, there were no significant differences in grey matter volume changes between groups. Significant correlations between brain activations and both clinical severity and age at disease onset were observed in FRDA individuals only at 24 months. There was significant longitudinal decline in Trail Making Test (TMT) difference score (B-A) in individuals with FRDA, compared with controls. These findings provide the first evidence of increased longitudinal activation over time in the cerebral cortex in FRDA, compared with controls, despite comparable working memory performance. This finding represents a possible compensatory response in the ventral attention network to help sustain working memory performance in individuals with FRDA.

Keywords Friedreich ataxia · Compensation · fMRI · Functional activation · Working memory · Longitudinal

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s12311-019-01094-6>) contains supplementary material, which is available to authorized users.

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Introduction

Friedreich ataxia (FRDA) is an autosomal recessive neurodegenerative disorder, the most common of all the inherited ataxias, with neuropathology mainly expressed in the spinal cord and dentate nuclei of the cerebellum [1]. However, functional and structural abnormalities in the cerebellar cortex, cerebral cortex and subcortical structures have also been reported in magnetic resonance imaging (MRI)-based studies [2–8]. The most salient presenting features of FRDA include motor incoordination and dysarthria.

While FRDA is not associated with dementia or profound cognitive disturbances, subtle behavioural abnormalities in cognitive functioning have been reported using targeted neuropsychological tests [2, 9–13]. Cross-sectional investigations, utilising task-based functional MRI (fMRI), have also shown differential patterns of cerebral and cerebellar functional activation during cognitive performance in individuals with

FRDA, compared with controls [3, 7]. Based on functional atlases of the cerebrum and cerebellum, defined using resting-state functional connectivity [14, 15] and corroborated by multi-task studies in healthy individuals [16, 17], a recent review indicated that cross-sectional functional abnormalities in FRDA were most consistently reported in regions corresponding to the ventral attention network (VAN) [7]. Previous studies have included investigations of cognitive control, verbal fluency and working memory and collectively reported aberrant activity and functional connectivity within and between cerebellar and lateral prefrontal brain regions within the VAN [6, 8, 10, 13]. Critically, these functional changes were associated with increased clinical severity and poorer behavioural performance in individuals with FRDA. However, the longitudinal trajectory of cognitive functioning and the integrity of underlying brain activation to support such functions, remains unknown in FRDA.

The primary aim of the present study was to investigate the role of the VAN in modulating task performance during working memory demands over 24 months in individuals with FRDA, compared with controls. We performed a longitudinal fMRI study of working memory function, via the use of an N-back task [18], using data from IMAGE-FRDA [4]. In light of previous longitudinal studies in other neurodegenerative diseases [19], we predicted that individuals with FRDA would show increased functional activation over time, compared with controls, indicative of a compensatory response. Moreover, we investigated whether the rate of such functional change over time was associated with clinical measures of disease severity and neurocognitive performance.

Materials and Methods

Participant Characterisation

The baseline IMAGE-FRDA dataset included 37 control participants, with no history of neurological or psychiatric diseases, and 33 individuals with genetically confirmed FRDA (homozygous for a GAA expansion in intron 1 of *FXN*), recruited from the Monash Medical Centre Friedrich Ataxia Clinic, Victoria, Australia [4].

Table 1 represents the demographic and clinical characteristics at each testing session, baseline and 24 months, in individuals with FRDA and controls. A two-sample *t* test was applied for group comparison of data with normal distribution and the remaining group differences were assessed with Mann-Whitney *U* test. Control participants were matched to individuals with FRDA for age and gender, although controls showed significantly higher educational attainment using Mann-Whitney *U* test (Table 1).

Follow-up data was collected at 24 months. Six subjects were lost to attrition, one was excluded due to poor

performance on the N-back task (<75% task accuracy) at follow-up, six had excessive motion, two fell asleep during scanning, and for six there was a data acquisition error. The final dataset for the current longitudinal investigation consisted of 21 individuals with FRDA and 28 controls. The study was approved by the Monash Health Human Research Ethics Committee. All participants provided written informed consent.

FRDA clinical severity was examined using the Friedreich Ataxia Rating Scale (FARS; [20]) at both time-points (Table 1). The FARS was scored out of 167, with a greater score indicating greater disease severity. Other clinical measures included disease duration at baseline, age at disease onset, and GAA repeat lengths on the smaller (GAA1) and larger (GAA2) alleles. While clinical data, such as age of onset, GAA1 and GAA2 repeat length did not change over time, the FARS score significantly increased by 6.7 points at 24 months, compared with baseline.

A brief neurocognitive battery was used to characterise the groups, including digit span forward and digit span backward tests [11], Hayling's sentence completion test [9], Stroop's test [21] and Trails Making Test, Parts A and B [22]. For the Trail Making Test, the difference in time (seconds) taken to complete Part B from Part A was subtracted to derive the cognitive component (e.g., this removes bias due to differences in upper extremity motor speed). Henceforth, we will term this as Trails Making Test (TMT) difference score (B-A) [9, 23]. These neurocognitive assessments were selected based on previous evidence of their sensitivity in FRDA [9] and relevance to the current fMRI task [4]. We applied analysis of covariance (ANCOVA) to assess group differences between the performance of individuals with FRDA and controls, at baseline, 24 months and longitudinal change over time, while correcting for age, gender and years of education (Table 2).

N-Back Working Memory Task

During the fMRI sessions, and at each time-point, participants performed an N-Back Working Memory Task, with letters as targets, consisting of a '0-back' (active baseline condition) and a '2-back' condition (high cognitive load). Full details are available from a previous publication [4]. Reaction time (RT) and task accuracy were recorded during fMRI data acquisition and the mean RT, reaction time variability (SD) and mean accuracy were computed. We performed ANCOVA, corrected for age, gender and years of education, to assess group differences between FRDA and controls at baseline, 24 months and longitudinal change over time.

MRI Acquisition

All individuals were scanned using a 3-Tesla Siemens Skyra with a 32-channel head coil. High-resolution T1-weighted

Table 1 Demographic and clinical characteristics across both testing points (baseline and 24 months) in individuals with FRDA and controls

		FRDA (<i>n</i> = 21)	Controls (<i>n</i> = 28)	Statistic	<i>p</i> value
Demographics					
Age (years)	Baseline	35.23 ± 2.65	38.41 ± 2.53	U = 241.00; Z = -1.07	0.28
Gender (f, m)	Baseline	6, 15	14, 14	$\chi^2(1) = 2.28$	0.13
Education (years)	Baseline	14.38 ± 0.41	16.57 ± 0.42	U = 138.50; Z = -3.21	< 0.01
	24 months	15.5 ± 0.47	17.48 ± 0.48	T (47) = 3.51	0.01
Clinical data					
Disease duration (years)	Baseline	13.83 ± 1.49	—	—	—
Age of onset (years)	Baseline	21.24 ± 2.06	—	—	—
GAA1 repeat length	Baseline	476.14 ± 40.09	—	—	—
GAA2 repeat length	Baseline	830.81 ± 57.21	—	—	—
Disease severity, FARS	Baseline	71.21 ± 6.48*	—	—	—
	24 months	77.94 ± 6.47*	—	—	—

Data are expressed as mean ± SEM; FARS, Friedreich ataxia rating scale; GAA, length of the abnormal GAA repeat in intron 1 of the FXN gene in the smaller (GAA1) and larger (GAA2) alleles; *paired samples *t* test $p = 0.002$; two-sample *t* test was applied for group comparison of data with normal distribution (remaining group differences were assessed with Mann-Whitney *U* test); significant group differences at $p < 0.05$ are set in italics

images were acquired, over 3.5 min, using magnetization prepared rapid gradient-echo (MP-RAGE) imaging with TE/TR = 2.55/1540 ms, flip = 9°, matrix size = 256 × 256, 208 sagittal slices and 1.0-mm isotropic voxels. Functional images were obtained using a gradient-echo echo-planar imaging sequence (GRE-EPIs) with TE/TR = 30/2500 ms, matrix size = 64 × 64, 44 slices, in-plane resolution = 3 × 3 mm² and slice thickness = 3 mm. Two runs, each consisting of 119 functional volumes, were acquired. At follow-up, data was acquired with the same scanner and using identical acquisition parameters.

Functional MRI Analysis

For each participant, at each time-point, the data were preprocessed as follows: (1) temporal registration to the middle slice of each functional volume, (2) spatial alignment to the first volume of each run, (3) co-registration to the T1-weighted structural image of each time-point, (4) skull-stripping, segmentation and nonlinear normalisation of the T1 images to Montreal Neurological Institute (MNI) anatomical space for the cerebrum and the spatially unbiased infratentorial template (SUIT) for the cerebellum, and (5) spatial smoothing by convolution with an isotropic Gaussian kernel of 5-mm full-width at half-maximum (FWHM). These fMRI preprocessing steps and the following individual-level statistical modelling, were performed using Statistical Parametric Mapping, SPM12 (Functional Imaging Laboratory, UCL, UK; <http://www.fil.ion.ucl.ac.uk/spm/>) and SUIT (www.diedrichsenlab.org/imaging/suit.htm) toolboxes for MATLAB.

Mixed-effects general linear models (GLM) were used to assess task-related functional activation, separately for each run, participant and time-point. The ‘0’- and ‘2’-back

conditions were coded as individual predictors for the fMRI time series. Additional regressors, modelling task instruction periods, motor effects (due to task-related button presses) and working memory ‘ramping’ effects were included to account for variance of noninterest (see previously reported cross-sectional study for full details [4]). Head movement parameters (3 planes of translation; 3 axes of rotation) were also included as covariates in the general linear model to robustly and conservatively account for motion. Task-related functional activation was estimated during 2-back, compared with 0-back, at the single subject level.

Contrasts at the individual level were used to determine the blood oxygen level-dependent (BOLD) change in ‘2-back’ minus ‘0-back’ functional activity at each time-point. These contrast maps were entered into group-level mixed-effects general linear models (GLM) to infer within- and between-group cross-sectional and longitudinal differences. Age, gender and years of education were controlled for in all group comparisons. Statistical thresholds were corrected for multiple comparisons (cluster-based family-wise error (FWE)-corrected $p < 0.05$) using nonparametric permutation (SnPM toolbox for SPM (<http://warwick.ac.uk/snpm>); cluster-forming threshold, $p = 0.05$).

Group-level inferences were first constrained to an a priori mask generated based on the overlap of an atlas of the VAN [14, 21] and the task-related functional activations at baseline (see Supplementary Materials and Fig. S1 for further details). The a priori mask included the following cerebral cortical regions: precentral gyrus, superior frontal gyrus, inferior frontal gyrus, pars opercularis, supplementary motor area, supramarginal gyrus, middle temporal gyrus, midcingulate area, medial frontal gyrus, insula, and precuneus (Fig. S1). The mask also included cerebellum crus 1, cerebellum VI,

Table 2 Neurocognitive performance over time, and at both testing points (baseline and 24 months) in individuals with FRDA and controls. The *p* values are corrected for age, gender and years of education. The reported comparisons at each time-point, undertaken for further qualification and exploration, have been adjusted for multiple comparisons

		FRDA (<i>n</i> = 21)	Controls (<i>n</i> = 28)	Statistic	<i>p</i> value	FDR-corrected <i>p</i> value
Working memory	Digit span forward	Δ -0.43 ± 0.36	-0.25 ± 0.43	$F(4, 44) = 1.53$	0.21	—
	Baseline	11.29 ± 0.48	12.25 ± 0.54	$F(4, 44) = 0.91$	0.46	0.48
	24 months	10.86 ± 0.46	12.00 ± 0.47	$F(4, 44) = 1.31$	0.28	0.40
Digit span backward	Digit span backward	Δ 0.00 ± 0.47	0.93 ± 0.44	$F(4, 44) = 0.50$	0.74	—
	Baseline	6.86 ± 0.49	8.21 ± 0.46	$F(4, 44) = 1.39$	0.25	0.40
	24 months	6.86 ± 0.46	9.14 ± 0.51	$F(4, 44) = 2.82$	0.04	0.10
Executive function	Haylings	Δ 0.05 ± 0.39	0.25 ± 0.19	$F(4, 44) = 1.48$	0.22	—
	Baseline	6.24 ± 0.18	6.25 ± 0.17	$F(4, 44) = 1.08$	0.38	0.47
	24 months	6.29 ± 0.31	6.50 ± 0.17	$F(4, 44) = 1.71$	0.16	0.32
Stroop	Baseline	55.76 ± 1.04	54.9 ± 61.20	$F(4, 44) = 3.59$	0.01	0.05*
	Baseline	55.76 ± 1.04	54.9 ± 61.20	$F(4, 44) = 3.59$	0.01	0.05*
	24 months	58.47 ± 1.40	56.3 ± 61.21	$F(4, 44) = 3.25$	0.02	0.06*
Visual attention and task switching	Trail Making Test (s) (TMT) difference score (B-A)	Δ 16.67 ± 7.44	-5.21 ± 2.66	$F(4, 44) = 3.10$	0.02	—
	Baseline	45.47 ± 8.72	31.21 ± 3.52	$F(4, 44) = 0.88$	0.48	0.48
	24 months	62.14 ± 9.47	26.00 ± 2.56	$F(4, 44) = 4.62$	< 0.01	0.01

Data are expressed as mean \pm SEM; significant group differences at $p < 0.05$ are set in italics; Δ , over 24 months; TMT, Trail Making Test Part B (s) minus Part A (s); *trending FDR-corrected *p* values

cerebellum VIII, cerebellum IX and cerebral vermis VI and VII regions (Fig. S1). This mask thus comprised a targeted set of brain regions relevant to the task and within brain areas hypothesised to be maximally impacted by FRDA. Further exploratory whole-brain analyses were also undertaken.

Grey Matter Analysis

To determine whether significant longitudinal between-group activation differences were associated with cortical atrophy, Voxel-based morphometry (VBM) was applied to the structural MRI data. The VBM analysis was performed using the computational anatomy toolbox (CAT12) (<http://dbm.neuro.uni-jena.de/cat12/>), SPM12 and SUI toolboxes for MATLAB.

For each participant, the raw T1-weighted images were preprocessed as follows: (1) the scans from cross-sectional and follow-up time-points were intra-registered and bias-corrected; (2) the images were segmented into grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF); (3) all images were normalised into MNI anatomical space for the cerebrum and SUI space for the cerebellum, with the normalised images modulated to correct volume changes by the Jacobian determinants; (4) spatial smoothing was applied with a 5-mm FWHM Gaussian filter; and (5) the total intracranial volume in MNI space was estimated for each time-point in order to correct for different head size and volume.

The interaction between Group and Time were tested using the flexible factorial statistical model including age, gender and total intracranial volume as covariates. The results were thresholded at FWE-corrected $p < 0.05$ (cluster-forming

threshold $p < 0.01$) across the whole brain within the cerebellum and the a priori mask of interest (defined above).

Correlation Analysis

In individuals with FRDA, linear relationships between functional activity (both cross-sectional and longitudinal change) and clinical measures were assessed using Pearson's and partial correlations for each brain region that showed longitudinal differences in brain activation between groups. Similar correlations between functional activity (both cross-sectional and longitudinal change) and neurocognitive tests were also undertaken.

Results

N-Back Working Memory Task

There were no significant cross-sectional or longitudinal between-group behavioural differences for RT, SD or task accuracy for 2-back>0-back (Table 3).

Functional Activations and GM Atrophy

Working memory task-related activations (2-back>0-back) in individuals with FRDA and controls, at baseline and 24 months (in the a priori mask; Fig. S1), are presented in Fig. 1 and Table 4.

In the FRDA group, significant task-related activations in the a priori mask were localised at both time-points in the

Table 3 N-back working memory task performance over time and across both testing points (baseline and 24 months) in individuals with FRDA and controls. The *p* values are corrected for age, gender and years of education

		FRDA (<i>n</i> = 21)	Controls (<i>n</i> = 28)	Statistic	<i>p</i> value
N-Back Task (2-Back > 0-Back)					
RT (ms)	Δ	-30.60 ± 27.28	-22.68 ± 18.07	F (4,44) = 0.35	0.84
	Baseline	91.16 ± 19.98	79.27 ± 13.36	F (4,44) = 0.56	0.69
	24 months	80.79 ± 21.58	72.05 ± 14.06	F (4,44) = 0.41	0.80
SD (ms)	Δ	-12.21 ± 23.37	0.10 ± 15.15	F (4,44) = 0.27	0.89
	Baseline	70.77 ± 13.39	83.0 ± 14.71	F (4,44) = 0.60	0.66
	24 months	58.56 ± 18.13	83.12 ± 14.12	F (4,44) = 0.39	0.81
Accuracy (%)	Δ	0.74 ± 0.48	0.09 ± 0.66	F (4,44) = 0.52	0.72
	Baseline	-1.87 ± 0.71	-1.10 ± 0.22	F (4,44) = 0.86	0.50
	24 months	-0.43 ± 0.36	-0.25 ± 0.43	F (4,44) = 1.70	0.17

Data are expressed as mean ± SEM; RT, reaction time magnitude; SD, reaction time variability; Δ, over 24 months

bilateral supplementary motor area, and left insula and inferior frontal gyrus (pars triangularis and pars opercularis; IFG). There were no significant activations in the cerebellar cortex. There was a significant within-group increase of activation over time in the right IFG and insula (Table 4).

In the control group, significant task-related activations in the a priori mask were evident at both time-points in the bilateral insula/IFG and the supplementary motor area in the cerebral cortex, as well as bilateral lobule VI and crus I in the cerebellar cortex (Table 4). There were no significant within-group changes of activation over 24 months.

As illustrated in Fig. 2 and Table 5, compared with controls, the FRDA group showed greater change of functional activation over time in bilateral insula and IFG. This between-group difference was driven by significantly increased activity in individuals with FRDA over time, with no change in controls (Fig. 2b).

There were no additional longitudinal between-group differences evident in either whole-brain or cerebellum comparisons.

Whole-brain VBM analysis revealed no significant longitudinal change in GM atrophy in individuals with FRDA, compared with controls. There were also no longitudinal between-group differences in GM atrophy evident in the a priori mask or the cerebellum.

Neurocognitive Tests

Table 2 presents neurocognitive performance over time, and at both testing points (baseline and 24 months), in individuals with FRDA and controls. The reported comparisons at each time-point, which were undertaken for further qualification and exploration, have been corrected for multiple comparison using false discovery rate (FDR) estimation. At each time-point, scores on digit span forward or backward tests yielded no significant differences between individuals with FRDA and controls. There were also no significant longitudinal differences between individuals with FRDA and controls across either task (i.e., forwards or backwards). No significant group differences were evident in the Hayling sentence completion test, at each time-point or longitudinally. In addition, there was

Fig. 1 Significant within-group cross-sectional functional activations (2-Back>0-Back) in the a priori mask (Fig. S1) in individuals with FRDA and controls, at baseline and separately at 24 months follow-up; L/R, left/right

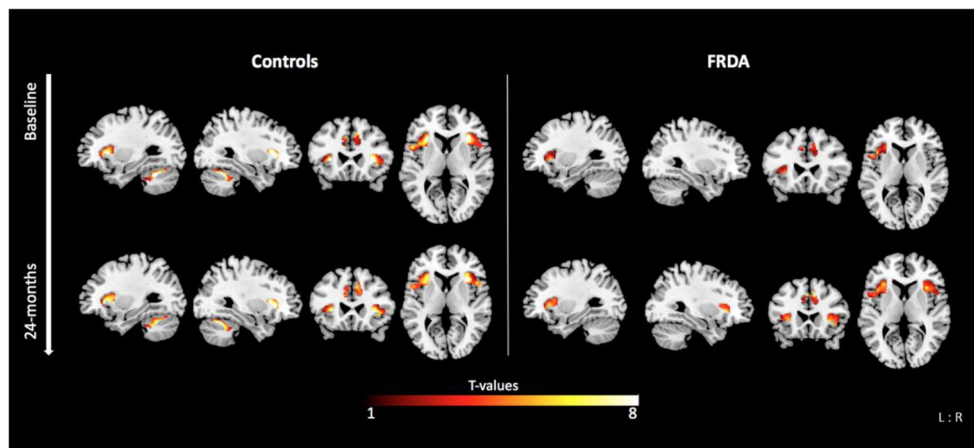


Table 4 Brain regions defined in automated anatomical labelling template, showing significance within-group difference in functional activation over time, as well as separately for baseline, and 24 months

Regions	BA	Side	Coordinates			T_{max}
			<i>x</i>	<i>y</i>	<i>z</i>	
Δ Controls						
—						
Controls (baseline)						
Cerebellum VI	37	R	34	−52	−30	13.17
Cerebellum VI	37	L	−32	−52	−30	13.20
Insula	13	R	32	20	4	12.67
Insula	47	L	−30	26	0	10.20
Inferior frontal gyrus, pars opercularis	44	R	58	14	18	5.26
Inferior frontal gyrus, pars opercularis	44	L	−50	8	20	7.32
Supplementary motor area	32	R	8	12	50	9.49
Supplementary motor area	6	L	−4	6	58	11.06
Controls (24 months)						
Cerebellum crus 1		L	−36	−48	−36	12.67
Cerebellum VI	19	R	28	−60	−26	10.16
Cerebellum VI	37	L	−32	−54	−30	8.91
Insula	13	R	32	18	8	10.06
Insula	47	L	−30	26	0	10.20
Inferior frontal gyrus, pars opercularis	13	R	48	14	4	8.93
Supplementary motor area	6	R	8	12	52	8.69
Supplementary motor area	32	L	−4	12	50	9.55
Δ FRDA						
Insula	48	R	36	16	−6	4.34
Inferior frontal gyrus, pars opercularis	45	R	42	22	6	4.07
FRDA (baseline)						
Midcingulate area	32	R	8	16	44	6.91
Midcingulate area	32	L	−6	12	44	8.04
Supplementary motor area	6	L	−4	2	64	7.15
Insula	13	L	−40	16	−2	6.10
FRDA (24 months)						
Midcingulate area	32	R	8	20	44	8.70
Supplementary motor area	32	L	−0	12	52	10.76
Medial frontal gyrus	32	L	−4	20	42	7.39
Insula	47	R	38	18	−4	7.57
Insula	47	L	−34	18	−2	6.46
Inferior frontal gyrus, pars opercularis	44	R	50	12	14	3.90

Results are cluster corrected at $p < 0.05$. T_{max} , maximum t value for the anatomical area; BA, Brodmann area; Δ , over 24 months

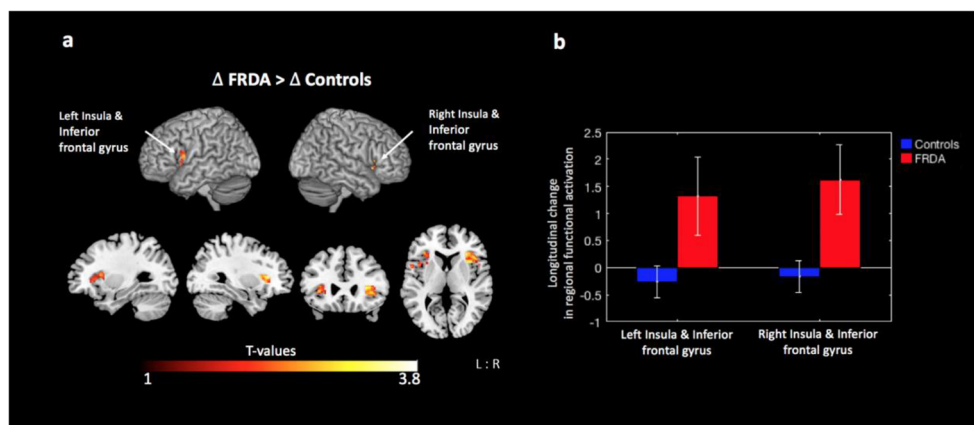
a trend for individuals with FRDA to perform worse than controls in the Stroop interference test at each time-point; these differences, however, did not reach significance. Furthermore, no significant longitudinal between-group differences were reported. For the TMT difference score (B-A), there was a significant difference at 24-month follow-up, with individuals with FRDA showing poorer performance, compared with controls. However, this effect was not observed at baseline. In addition, significant longitudinal change

($p < 0.05$) was found only for TMT difference score (B-A) between individuals with FRDA and controls, as a result of controls improving their performance (faster) and individuals with FRDA performing worse (slower) over time.

Correlations

There were no significant correlations between longitudinal change in 2-back>0-back task performance measurements

Fig. 2 **a** Significant between-group differences in longitudinal changes (Δ) in the a priori mask (cluster-level family-wise error (FWE) corrected $p < 0.05$); L/R, left/right. **b** Plots of Δ fMRI activity in the regions depicted in (a) (error bars = SEM)



(RT, SD or task accuracy) and longitudinal change in brain activation in the bilateral insula and IFG for either group.

At baseline, no significant correlations between functional activation and clinical scores were observed in cerebral regions that showed longitudinal change in functional activity (bilateral insula and IFG) in individuals with FRDA. At 24 months, task-related activation in the right insula and IFG showed a negative correlation with the FARS score (right $r = -0.47$, $p = 0.03$). Activation at 24 months also correlated positively with age at disease onset (left $r = 0.58$, $p = 0.008$; right $r = 0.42$, $p = 0.056$). The clinical correlations are illustrated in Fig. 3. No significant association between longitudinal fMRI and clinical scores were evident.

In both the FRDA and control groups, no significant correlations were observed between longitudinal change in neurocognitive measures and change in brain activation over time.

Discussion

This is the first longitudinal fMRI study to assess functional brain activation changes over time in FRDA. We report

increased functional activation in the VAN, including the bilateral insula, pars triangularis and pars opercularis in individuals with FRDA, compared with controls, over a 24-month follow-up period. The increased cerebral activity was observed alongside comparable working memory performance with controls, despite worsening of disease severity over time.

One possible explanation for the increased activation in cerebral activity may be due to the involvement of compensatory mechanisms. Brain compensation refers to the ability of the brain to increase fMRI activity in task-specific networks and/or to recruit additional cortical regions to help support behavioural performance (Barulli & Stern, 2013). Numerous functional neuroimaging studies, in a number of neurodegenerative disorders, have shown that patients exhibit increased fMRI activity and recruit additional brain regions to maintain a comparable level of behavioural performance with controls, including in Huntington's disease [19, 24–26]. This finding is also consistent with previous cross-sectional findings of increased cerebro-cerebral functional connectivity in the context of impaired cerebello-cerebral connectivity [2, 13].

In accordance with our previous cross-sectional working memory findings [4], we observed disease-related cross-sectional dysfunction in regions of the VAN, including in the

Table 5 Brain regions defined in automated anatomical labelling template, showing significant between-group difference in change functional activation over time during working memory performance

Regions	BA	Side	Coordinates			T_{max}
			x	y	z	
Δ FRDA > Δ Controls						
Insula	13	R	36	16	-6	3.79
Insula	13	L	-28	14	12	3.36
Inferior frontal gyrus, pars opercularis	45	R	42	20	10	3.86
Inferior frontal gyrus, pars opercularis	13	L	-48	12	2	2.81
Inferior frontal gyrus, pars triangularis	13	R	30	28	8	3.36
Inferior frontal gyrus, pars triangularis	47	L	-34	30	4	2.81

Results are cluster corrected at $p < 0.05$. BA, Brodmann area; x, y, z = MNI coordinates at cluster peak; T_{max} , maximum t value for the anatomical area; Δ , over 24 months

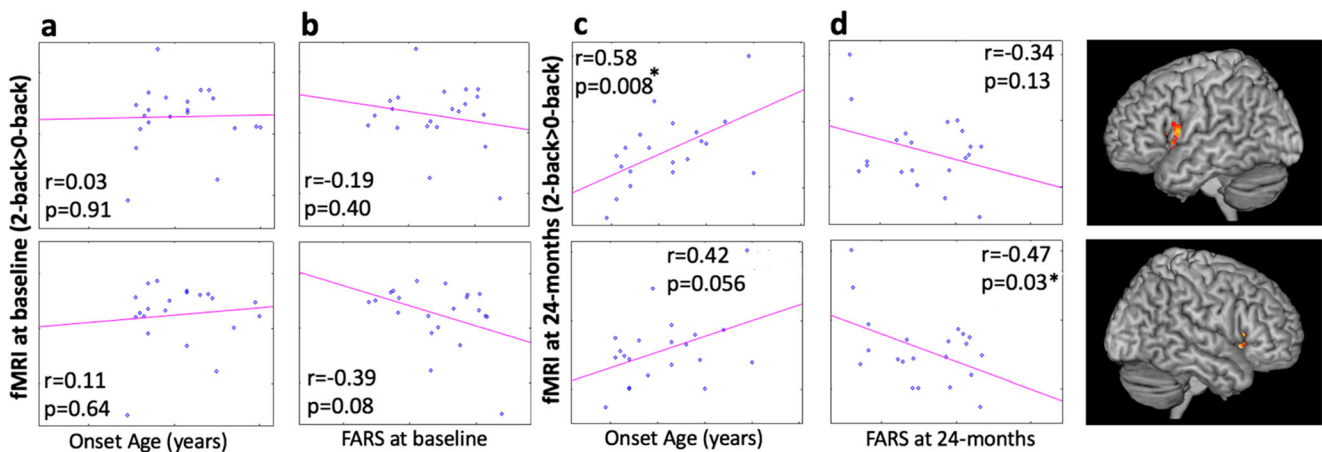


Fig. 3 Linear correlations between clinical measures and mean functional activation in brain areas showing significant disease-related longitudinal changes (top: left insula and inferior frontal gyrus; bottom: right insula and inferior frontal gyrus; see Fig. 1). The scatterplots reflect (a) mean activation at baseline versus age at disease onset, (b) mean activation at

baseline versus disease severity (FARS) at baseline, (c) mean activation at 24 months versus age at disease onset, and (d) mean activation at 24 months and FARS at 24 months. Correlations were significant at 24 months, but not at baseline. Pearson's correlations coefficients are reported (* $p < 0.05$)

cerebrum and cerebellum in individuals with FRDA, compared with controls [4, 5]. However, significant longitudinal changes were observed specifically in the cerebrum, but not cerebellum, in the FRDA cohort compared with controls. It is possible that stage of disease may impact task-related functional activity in individuals with FRDA. Importantly, we note that our sample had a mean onset age of 21 years and 13 years average disease duration. These cerebral-specific changes may therefore be representative of later disease stages, while it is possible that cerebellar functional changes may be more pronounced during the earlier stages of disease (when atrophic changes are more notable). Further investigation with larger datasets, comprising a broader range of disease expression (including paediatric individuals), is required to determine the impact of stage of disease on functional activation in FRDA.

Interestingly, regions that showed increased activity also had a significant correlation between the FARS score and functional activation at 24 months, but not at baseline. However, the results did not reveal a linear link between longitudinal task-related functional activations in FRDA and clinical measures. Accordingly, linear models may not explain the complex biology of the disease progression [27, 28]. Further exploration of the association between longitudinal cerebral change of activation and disease severity in different subgroups of disease onset (e.g., early-onset and late-onset [29]) would be beneficial for future research.

The present study found no cross-sectional or longitudinal behavioural differences between individuals with FRDA and controls for working memory (N-back task; digit span forward and backward tests) or for executive function (Hayling's test). Significant cross-sectional between-group differences were evident in TMT difference score (B-A) at 24 months, and a

trend in Stroop at both time-points, while the only neurocognitive test to show progressive 24-month longitudinal decline in individuals with FRDA was the TMT difference score (B-A). These results indicate that visual attention and task switching abilities may be affected in individuals with FRDA and progress with disease advancement. Many previous studies in FRDA have not reliably shown neurocognitive impairment on the digit span backward and forward tests [2] or the Stroop test [2, 9]. The differences in results between the reported neurocognitive findings and similar cross-sectional studies in FRDA [9] may be driven by differences in the size and characteristics of the cohorts. Further research is required to investigate longitudinal trajectories of neurocognitive deficits in FRDA.

The limitations of this study include its relatively small sample size, which is common in single-site studies of rare diseases. Multi-centre collaboration would increase the statistical power of future studies going forward [7]. Our cohort included adult individuals with FRDA who had a minimum disease duration of five years. Previous research shows that disease duration has a linear correlation with clinical and functional measures in the first 25 years of the disease before these stabilise [27]. Given more than 90% of the recruited individuals with FRDA had a disease duration of less than 25 years, we were able to capture important neuroanatomical changes associated with disease progression and functional performance over time.

Conclusion

For the first time, we report longitudinal increased brain activation in the cerebrum (VAN) in individuals with FRDA,

alongside comparable working memory performance with controls. These findings may reflect a possible compensatory mechanism associated with disease progression in individuals with FRDA. These important insights allow us to move one step closer in understanding brain reorganisation in FRDA and how functional imaging methods could be used to track cortical changes in response to therapeutic interventions during early drug development [30].

Acknowledgements We especially acknowledge the volunteers who participated in this research, as well as the Friedreich Ataxia Research Alliance (USA) and the Friedreich Ataxia Research Association (Australasia) for their support of our work.

Funding Information This study was funded by the National Health and Medical Research Council (NHMRC) (Project Grant 1046037). IHH is funded by a NHMRC Fellowship 1106533. LC is funded by a MRFF Career Development Fellowship APP1143098.

Compliance with Ethical Standards

The study was approved by the Monash Health Human Research Ethics Committee. All participants provided written informed consent.

Conflict of Interest The authors declare that they have no conflict of interest.

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