Fronto-Cerebellar Dysfunction and Dysconnectivity Underlying Cognition in Friedreich Ataxia: The IMAGE-FRDA Study

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Abstract: Friedreich ataxia (FRDA) is a progressive neurodegenerative disorder defined by pathology within the cerebellum and spinal tracts. Although FRDA is most readily linked to motor and sensory dysfunctions, reported impairments in working memory and executive functions indicate that abnormalities may also extend to associations regions of the cerebral cortex and/or cerebello-cerebral interactions. To test this hypothesis, 29 individuals with genetically confirmed FRDA and 34 healthy controls performed a verbal *n*-back working memory task while undergoing functional magnetic resonance imaging. No significant group differences were evident in task performance. However, individuals with FRDA had deficits in brain activations both in the lateral cerebellar hemispheres, principally encompassing lobule VI, and the prefrontal cortex, including regions of the anterior insular and rostro-lateral prefrontal cortices. Functional connectivity between these brain regions was also impaired, supporting a putative link between primary cerebellar dysfunction and subsequent cerebral abnormalities. Disease severity and genetic markers of disease liability were correlated specifically with cerebellar dysfunction, while correlations between behavioural performance and both cerebral activations and cerebello-cerebral connectivity were observed in controls, but not in the FRDA cohort. Taken together, these findings support a diaschisis model of brain dysfunction, whereby primary disease effects in the cerebellum result in functional changes in downstream fronto-cerebellar networks. These fronto-cerebellar disturbances provide a putative biological basis for the nonmotor symptoms observed in

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INTRODUCTION

Friedreich ataxia (FRDA) is the most common inherited ataxia [Schulz, et al., 2009]. It is caused by mutations in *FXN*, with about 96% of affected individuals being homozygous for a GAA repeat expansion in intron 1 of the gene, leading to central and peripheral neuropathy, cardiomyopathy, and endocrine dysfunction [Pandolfo, 2009]. Within the brain, FRDA is defined by progressive degeneration of cerebellar tissue, most notably within the deep dentate nuclei [Franca, et al., 2009; Koeppen, et al., 2011a]. Cerebellar pathology, in conjunction with spinal tract degeneration and peripheral neuropathy, is readily linked to the hallmark gait and limb coordination disturbances that characterize the illness [Corben, et al., 2012; Pandolfo, 2009]. Deficits in higher-order cognitive functioning have also been described [Corben, et al., 2006], yet the neurobiological correlates underlying cognitive disturbances remain poorly understood. Characterizing the pathophysiology of nonmotor disturbances in FRDA is critical to developing more complete models of the disorder, and to ensuring that the full constellation of symptomatology is recognized both in therapeutic and research contexts [Corben, et al., 2012].

A range of higher-order cognitive deficits have been reported in FRDA, including impairments of selective and sustained attention, working memory, response inhibition, and cognitive initiation [Corben, et al., 2011a; de Nobrega, et al., 2007; Fielding, et al., 2010; Hocking, et al., 2014; Kloppe, et al., 2011; Nieto, et al., 2012; Wollmann, et al., 2002]. Although reported dysfunction is often subtle, deficits are clearly associated with measures of clinical severity and factors related to disease expression, including genetic markers and age at disease onset [Corben, et al., 2011a; Kloppe, et al., 2011; Nachbauer, et al., 2014; Nieto, et al., 2013]. These findings are in line with lesion studies that highlight the consequence of cerebellar damage for executive functioning [Brunamonti, et al., 2014; Tedesco, et al., 2011; Ziemus, et al., 2007], and work in healthy populations explicating the role that the cerebellum plays in facilitating fluid and dynamic human cognition [Buckner, 2013; E, et al., 2014; Schmahmann and Caplan, 2006].

Functional neuroimaging studies indicate that regions of the cerebellar cortex most responsive to cognitive demands—namely lobules VI and VII [Stoodley and Schmahmann, 2009; Stoodley, et al., 2012]—interact intimately with prefrontal and parietal association cortices of the cerebrum [Buckner, et al., 2011; Habas, et al., 2009]. It has been postulated

that cognitive disruptions in FRDA may, therefore, be the consequence of abnormal neural function that extends beyond the cerebellum [Corben, et al., 2012; Mantovan, et al., 2006]. This suggestion is formalized by the concept of focal functional diaschisis, whereby neural dysfunction manifests in anatomically intact brain regions distant from a primary lesion [Carrera and Tononi, 2014].

In support of diaschisis in FRDA, emerging evidence from magnetic resonance imaging (MRI) studies has demonstrated a loss of volume and axonal integrity within the superior cerebellar peduncles, which contain the ascending efferent fibers of the dentate nuclei [Akhlaghi, et al., 2011; Clemm von Hohenberg, et al., 2013; Corben, et al., 2014; Della Nave, et al., 2008b; Della Nave, et al., 2011; Pagani, et al., 2010; Rizzo, et al., 2011; Vieira Karuta, et al., 2015]. These anatomical changes result in reduced cerebellar innervation of widespread regions of the prefrontal cortex [Zalesky, et al., 2014]. In turn, preliminary evidence from functional MRI studies, undertaken in small cohorts of individuals with FRDA, suggests the presence of deficient or inefficient cerebral activity associated with motor and cognitive processes [Akhlaghi, et al., 2012; Georgiou-Karistianis, et al., 2012; Ginestroni, et al., 2012]. However, links between cerebellar abnormalities, changes in cerebello-cerebral connectivity, and putative dysfunction in the cerebral cortex remain hypothetical.

One powerful means of linking abnormal neural function with deficits in neural interactions involves the quantification of task-related functional connectivity, as defined by task-induced changes in the covariance of neural activity across discrete brain regions [O'Reilly, et al., 2012]. Functional dysconnectivity is thought to be a major contributor to cognitive disruption in brain disorders [Gillebert and Mantini, 2013; Sporns, 2014], and previous work using functional MRI has identified changes in cognition-related cerebello-cerebral functional connectivity in other disorders of the cerebellum [Passamonti, et al., 2011; Reetz, et al., 2012]. Investigating such phenomena in FRDA provides the means to extend concepts of focal functional diaschisis to also encompass connectional functional diaschisis, whereby changes in coupling between brain regions occur antero-grade to a lesion [Carrera and Tononi, 2014].

In this study, we utilize functional MRI and a visually-presented verbal *n*-back task to investigate the hypothesis that primary abnormalities in the cerebellum are associated with clinically-relevant neural dysfunction (i.e., focal diaschisis) and functional dysconnectivity (i.e., connectional diaschisis) in cerebello-cerebral networks relevant to higher-order cognition in FRDA.

TABLE I. Demographic, clinical, and task performance characteristics

Demographics	FRDA (N = 29)	Controls (N = 34)	Statistic	P-value
Age, years (Mdn [Range])	30.0 [18.2–56.3]	33.6 [18.8–62.1]	$U = 426, Z = -0.92$	$P = 0.36$
Gender (M, F)	16, 13	17, 17	$\chi^2(1) = 0.168$	$P = 0.68$
Education, years (Mdn [Range])	14.0 [11–18]	16.5 [13–22]	$U = 187, Z = -4.29$	$P < 0.001$
Clinical data				
Disease duration, years	15.4 ± 7.81	–	–	–
Age of onset, years	19.4 ± 9.01	–	–	–
GAA1 repeat length	546 ± 231	–	–	–
GAA2 repeat length	860 ± 251	–	–	–
FARS score	88 [19–119]	–	–	–
n-Back Task (2-Back > 0-Back)				
RT magnitude, ms (M $\pm$ SD)	103.5 ± 91.5	78.4 ± 72.7	$F(1,61) = 0.20$	$P = 0.66$
RT variance, ms (M $\pm$ SD)	78.7 ± 68.6	76.1 ± 73.9	$F(1,61) = 0.15$	$P = 0.70$
Accuracy, % (M $\pm$ SD)	-2.38 ± 4.22	-1.47 ± 1.85	$F(1,61) = 1.04$	$P = 0.31$

GAA1/GAA2, shorter/longer alleles of the *FXN* gene; FARS, Friedreich Ataxia Rating Scale; RT, Reaction Time; Inference is performed using non-parametric statistical tests due to violations of normality and/or equality of error variance (Mann-Whitney U-tests for demographics, Quade tests of covariance (controlling for age, gender, education) for *n*-back metrics).

MATERIALS AND METHODS

Participants

Data from 29 individuals with FRDA, homozygous for a GAA expansion in intron 1 of *FXN*, were included in analyses. Four additional participants with FRDA were excluded due to excessive movement (x2; see *fMRI Data Preprocessing*, below), periods of sleep (x1), or data acquisition errors (x1) during scanning. All individuals with FRDA were recruited from the Monash Medical Centre Friedreich ataxia clinic, Victoria, Australia. Fifteen of these participants were receiving pharmacological controls for cardiovascular disease, including ACE inhibitors, beta-blockers, and statins. Select participants were also prescribed: anticholinergics (x6); selective serotonin reuptake inhibitors (x2), benzodiazepines (x1), GABA agonists (x3), and insulin (x2); 10 participants were taking idebenone and one resveratrol.

Thirty-four age and gender-matched healthy control participants (CON) were recruited from the general community; 3 additional control datasets were excluded due to data acquisition errors (x2) and sleep (x1). All but 2 participants were right handed. Participants were recruited as part of IMAGE-FRDA, a large-scale longitudinal neuroimaging study based in Melbourne, Australia. This project was sanctioned by the Monash Health Human Research Ethics Committee; all participants gave informed, written consent prior to study participation.

Demographic and clinical information is reported in Table I. Clinical severity in individuals with FRDA was rated according to the Friedreich Ataxia Rating Scale (FARS) [Subramony, et al., 2005]. Participants also completed a neurocognitive battery and the Beck Depression Inventory (Table S1).

Behavioral Stimuli and Task Design

Cognitive load was manipulated using an *n*-back continuous performance working memory paradigm. The *n*-back

is a well-validated cognitive paradigm that is known to robustly activate cerebello-cerebral cognitive networks and provides for generalized manipulation of executive, maintenance, and attentional processes [E, et al., 2014; Owen, et al., 2005; Stoodley, et al., 2012].

Task stimuli consisted of letters presented individually, centered on a visual display for 500 ms and separated by a pseudorandomly varying interstimulus interval of 1250 ms, 1500 ms, or 1750 ms. The paradigm consisted of two task conditions: (i) a “0-back” active baseline condition requiring a button press when a prespecified letter appeared on-screen; and (ii) a “2-back” condition requiring a button press when the current letter was the same as that presented two letters previously (Fig. S1). Prior to scanning, all participants achieved an accuracy of at least 75% on a practice set of 2-back blocks. Full task details are available in Supporting Information.

Stimuli were presented using E-prime software (Psychological Software Tools, Pittsburgh), projected centrally onto a translucent screen and viewed through a head-coil mounted mirror. Responses were collected via Lumitouch™ fMRI optical response keypads (Photon Control Inc., BC, Canada).

MRI Data Acquisition

All participants were scanned using a 3 Tesla Siemens Skyra scanner (Siemens, Erlangen, Germany) with a 32 channel head coil at Monash Biomedical Imaging, Victoria, Australia. Each functional run was acquired over 5.2 mins and consisted of 119 whole-brain, gradient-echo echo-planar images (GRE-EPIs) comprising 44 interleaved, contiguous axial slices (TR = 2500 ms; TE = 30 ms; flip angle = 90°; slice thickness = 3 mm; in-plane resolution = 3 × 3 mm; matrix = 64 × 64; field of view = 192 × 192 mm). A whole-brain T1-weighted magnetization-prepared rapid gradient-echo (MPRAGE) structural image was additionally

acquired over 3.5 mins for each participant (208 sagittal slices; 1.0 mm isotropic voxels; TR = 1540 ms; TE = 2.55 ms; flip angle = 9°; field of view = 256 × 256 mm; matrix = 256 × 256).

Behavioral Data Analysis

Statistical analyses were carried out using the Statistical Package for Social Sciences (ver. 20; SPSS®, IBM Corporation, Armonk, NY). For each participant, average reaction time magnitude (RT), reaction time variability (SD), and task accuracy were calculated for each task condition. Only correct task trials were included in RT and SD analyses. All analyses were performed using task-related difference scores (i.e., 2-back minus 0-back) in order to isolate cognitive effects of interest. Due to violations of normality and equality of error variance, group differences were inferred using nonparametric signed-rank tests of covariance [Quade, 1967]. Age, gender, and years of education were included as covariates in all models. Within-group effects were assessed using parametric one-sample *t*-tests or nonparametric Mann-Whitney U-tests, as appropriate.

Clinical variables of interest included disease severity (FARS score), reported age at disease onset, disease duration, and the number of GAA triplet repeats in the smaller allele of *FXN* (GAA1). Due to the highly correlated nature of the clinical variables, dimension reduction was conducted using a Principal Components Analysis to ascertain a single variable (the first principal component) that maximally accounted for common variance between the four clinical measures. This variable, referred to hereafter as the *clinical index score*, accounted for 60% of this shared variance, and correlated with each clinical measure as follows: FARS, $r = 0.90$; Onset Age, $r = -0.67$; Duration, $r = 0.60$; GAA1, $r = 0.88$. This approach effectively reduced the number of multiple comparisons performed when undertaking exploratory Spearman correlations with the behavioural (RT and SD) and neuroimaging measures. Where significant associations were inferred, post-hoc assessments of each clinical variable were performed for disambiguation of the effect.

fMRI Data Preprocessing

Functional image processing and analyses were performed using SPM8 software (Functional Imaging Laboratory, UCL, UK; <http://www.fil.ion.ucl.ac.uk/spm/>). For each participant, the data were preprocessed as follows: (i) temporal registration to the middle slice of each functional volume; (ii) spatial alignment to the mean volume of each run; (iii) coregistration to the T1-weighted structural image; (iv) normalization to Montreal Neurological Institute (MNI) anatomical space using a diffeomorphic registration algorithm (DARTEL); (v) spatial smoothing using a Gaussian kernel of 5 mm full-width at half-maximum (FWHM); (vi) interpolation of large signal deviations (i.e., “spikes”) resulting from excessive volume-to-volume head motion (>0.8 mm/TR; ArtRe-

pair toolbox v4; <http://cibsr.stanford.edu/tools/human-brain-project/artrepair-software>; 2 participants with FRDA were excluded from further analyses as more than 25% of volumes were affected). Absolute head displacement did not exceed 3 mm in any plane for any participant. As described below, head motion parameters were also included as covariates in the general linear model. These latter steps were implemented to robustly and conservatively account for the tendency for greater trial-by-trial motion in the clinical cohort.

fMRI Data Analysis

Functional activations related to the cognitive manipulation were assessed using mixed-effects general linear modeling (GLM). For each run in each individual, the “0-back” and “2-back” task conditions were coded as individual predictors of the fMRI time series, alongside additional regressors accounting for known variance of noninterest (e.g., head motion; See Supporting Information for full details). Difference contrasts between the 2-back and the 0-back effects served to quantify the magnitude of task-related change in the fMRI signal.

Task-based functional connectivity was estimated using generalized psychophysiological interaction analyses (gPPI; [McLaren, et al., 2012]). For each individual, the design matrix described above was replicated, with the addition of 3 further predictors: (i) the timecourse of a seed region-of-interest, defined by a 3 mm sphere centered on the peak between-group task activation difference in the cerebellum; (ii) the cross-product of the seed regressor and the 2-back task regressor; and (iii) the cross-product of the seed regressor and the 0-back task regressor. Regression parameter estimates from (i) served to quantify the *static*, or task-invariant, connectivity between the seed region and all other voxels. Difference contrasts between (ii) and (iii) quantified task-related *dynamic* connectivity relevant to cognitive processes.

At the group-level, two-sample *t*-tests were used to infer population differences between each of these effects (cognition-related activations; task-invariant static connectivity; and task-related dynamic connectivity). These effects respectively correspond to the “main psychological effect,” the “main physiological effect,” and the “psycho-physiological interaction” of the PPI model. The statistical independence (orthogonality) of these factorial effects ensures that a group difference in one does not mandate a comparable effect in the others [Gerchen, et al., 2014]. Age, gender, and years of education were included as nuisance covariates in between-group comparisons. Statistical thresholds were corrected for multiple comparisons (cluster-based family-wise error corrected $P < 0.05$) using Monte Carlo simulations (Supporting Information).

Sequential Inference Procedure

A sequential inference procedure was used to inform masking of cerebral inference and selection of seed regions-of-interest for connectivity analyses, as follows:

Figure 1.

Cerebellar fMRI Task Activations. (Top) Significant task-related activations (2-back > 0-back; orange) in the control (CON) and clinical (FRDA) groups overlaid on coronal slices (Y-plane) of the cerebellar cortex (left) and dentate nuclei (right; probabilistic mask depicted in blue) in standard MNI space using neurological convention. **(Middle)** Significant between-group differences in task-relevant areas of the cerebellum; all areas show greater activation in the control group. No between-group differences

are evident in the dentate. **(Bottom)** Plots of fMRI effects for each condition and each group in the four regions (A–D) eliciting strongest disease-related effects in the cortex; A = Lobule VIIb; B = Lobule VI (motor); C/D = Lobule VI (cognitive). In the dentate, fMRI effects are plotted for regions eliciting maximal main task effects due to lack of between-group differences. Error bars = S.E.M.

Group differences in cerebellar activations were first inferred using the “Spatially Unbiased Infra-tentorial” (SUIT) template [Diedrichsen, 2006] and a probabilistic map of the dentate nuclei [Diedrichsen, et al., 2011].

Group differences in cerebral activations were then assessed, targeting cortical areas most strongly associated with cerebellar regions identified in step (i), using a cerebro-cerebellar functional connectivity atlas [Buckner, et al., 2011; Yeo, et al., 2011]; Fig. S2. The thalamus was isolated using the Harvard-Oxford atlas (<http://fsl.fmrib.ox.ac.uk/>).

Group differences in cerebello-cerebral functional connectivity were then examined using a seed region defined by the maximal group difference identified in step (i). Cerebral inference was masked as per step (ii).

Spearman correlations were employed to infer associations between regions/connections eliciting between-group differences (3 mm spheres centered at the peak voxel) and (i) the clinical index score in individuals with FRDA; and (ii) task-related measures of reaction time magnitude (RT) and reaction time variance (SD).

These targeted assessments were supplemented by unconstrained, whole-brain exploratory analyses (reported in Supporting Information).

RESULTS

Behavioral Data

For each of the FRDA and the CON groups, task-related cognitive loading (2-back > 0-back) was evidenced by significantly slowed reaction time (RT; FRDA: $t(28) = 6.1$, $P < 0.001$; CON: $t(34) = 6.3$, $P < 0.001$), increased reaction time variability (SD: FRDA: $Z = -4.4$, $P < 0.001$; CON: $Z = -4.3$, $P < 0.001$), and reduced task accuracy (FRDA: $Z = -2.9$, $P = 0.004$; CON: $Z = -4.0$, $P < 0.001$); see Table S2 for raw data.

However, no significant between-group differences were found on any of these measures (Table I), indicating that the cognitive aspects of the task were performed with relatively equal acuity by individuals with FRDA and healthy controls.

Cerebellar fMRI Activations

As illustrated in Figure 1, robust activations (2-back > 0-back) in the control group were evident bilaterally across lobule VI and crus I in the superior cerebellar cortex and within lobule VIIb of the inferior cortex (Table S3).

Figure 2.

Cerebral fMRI Task Activations. (Top) Task-related activations (2-back > 0-back; orange) and deactivations (blue) in the control (CON) and clinical (FRDA) groups in a constrained mask of the cerebral cortex (left; see **Fig S2** for masking details) and axial (Z-plane) slices of the thalamus (right; probabilistic mask depicted in blue) in standard MNI space. **(Middle)** Significant between-group differences in task-relevant areas of the cere-

brum; all areas show greater activation in the control group. **(Bottom)** Plots of fMRI effects for each condition and each group in the four regions (A–D) eliciting strongest disease-related effects in the cortex: A = rostralateral prefrontal cortex; B = anterior insula; C = middle insula; D = parietal operculum; Effects are also plotted for both hemispheres of the thalamus.

Activations were largely constrained within conventional anatomical boundaries defining these lobules, but spread across putative functional segregations between cognitive and motor areas of lobule VI [Buckner, et al., 2011; Stoodley, 2012]. In individuals with FRDA, significant activations were found in qualitatively similar areas, but with reduced spatial extent. Bilateral activations in dorsal and lateral regions of the dentate nuclei were also evident in both cohorts.

Quantitative between-group comparisons revealed significantly reduced fMRI activations in the FRDA group throughout these cerebellar cortical regions, with maximal between-group differences centering on cognitive regions of lobule VI, bilaterally (Fig. 1; Table S3). Predominantly right-lateralized group differences were also evident in lobule VIIb and motor areas of lobule VI. *Post-hoc* characterization of these findings indicates that group differences were driven specifically by aberrations manifesting at the 2-back cognitive load (Fig. 1). No significant between-group differences were evident in the dentate nuclei.

Cerebral fMRI Activations

Within the constrained cerebral mask, which largely conforms to the canonical salience/ventral attention network (Fig. S2), significant task-related activations were evident in both groups within bilateral regions of the rostralateral prefrontal cortices (rIPFC), anterior insulae, and medial prefrontal cortices encompassing areas of the dorsal anterior cingulate cortices and presupplementary motor areas (Fig. 2; Table S4). Deactivations in response to working memory demands within the mask were observed in bilateral regions of the middle/posterior insulae, and middle/posterior cingulate cortices (Fig. 2; Table S4). Thalamic activations were also observed throughout ventral and anterior aspects of the structure.

Significant between-group differences in these areas were found exclusively in the left hemisphere, with lesser task-related activations in the rIPFC, anterior insula, and ventrolateral thalamus, as well as greater deactivations in the middle insula and parietal operculum in individuals

Figure 3.

Cerebello-Cerebral Connectivity. Regions of the cerebral cortex (within the constrained anatomical mask; see Fig S1) eliciting significant **(A)** task-independent (static) functional connectivity (orange = positive covariance) and **(B)** task-dependent

(dynamic) connectivity (blue = reduced connectivity during 2-back versus 0-back). **(C)/(D)** Significant between-group differences in static and dynamic functional connectivity, respectively.

with FRDA (Fig. 2; Table S4). Notably, a subthreshold reduction in activation was also present in the right aIns ($x, y, z = 30, 18, 6$; cluster extent = 23; $t_{\max} = 3.6$). As in the cerebellum, group differences were driven specifically by activation differences related to the 2-back cognitive load condition (Fig. 2).

Cerebello-Cerebral Connectivity

The seed region-of-interest was defined by the peak group-difference in the cerebellar cortex, located in right lobule VI (see above). Task-invariant connectivity between the seed and masked regions of the cerebral cortex were robust in controls throughout the insular, rostrolateral prefrontal, and cingulate cortices bilaterally; comparable effects in the FRDA group were isolated to bilateral insular regions (Fig. 3; Table S5). Quantitative comparisons confirmed FRDA-related connectivity reductions in bilateral regions of the rIPFC and both anterior and middle cingulate cortices (Fig. 3; Table S5).

In addition to this generalized reduction in functional connectivity, individuals with FRDA displayed a significant reduction in normal task-related connectivity changes within many of these regions. In the control group, cognitive demands were associated with a decrease in connectivity between the cerebellar cortex and bilateral rIPFC, left

anterior insula, and anterior cingulate cortex, while no significant task-related dynamics were observed in FRDA (Fig. 3; Table S6). With the exception of the anterior cingulate cortex, quantitative between-group differences were evident in all areas (Fig. 3).

Clinical Correlations

In bilateral regions of lobule VI, the magnitude of functional activations correlated significantly with the clinical index score in the FRDA cohort (right: $\rho(29) = -0.40$; $P = 0.030$; left: $\rho(29) = -0.40$; $P = 0.033$). As illustrated in Figure 4, disambiguation of the clinical effect suggests that less task-related fMRI activation in these regions was associated with: greater FARS score (right: $\rho(29) = -0.36$, $P = 0.054$; left: $\rho(29) = -0.37$, $P = 0.047$), earlier age of onset (right: $\rho(29) = 0.54$, $P = 0.002$; left: $\rho(29) = 0.36$, $P = 0.052$), and longer GAA1 repeat length (right: $\rho(29) = -0.43$, $P = 0.019$; left: $\rho(29) = -0.28$, $P = 0.14$). These *post-hoc* correlation analyses were not corrected for multiple comparisons, and thus represent exploratory data trends.

Task-related activation in the right dentate nucleus was also significantly associated with the clinical index score (Fig. 4; $\rho = -0.46$; $P = 0.011$). This effect was most pronounced with respect to FARS score ($\rho(29) = -0.41$, $P = 0.026$) and GAA1 repeat length ($\rho(29) = -0.43$, $P = 0.020$). However, as reported

Figure 4.

Clinical Correlations. Linear relationships between disease severity (FARS), age at disease onset, and the abnormal genetic triplet repeat length (GAA1) and the magnitude of task-related fMRI activations in right lobule VI (top row), left lobule VI (middle row), and the right dentate nucleus (bottom row) in the FRDA cohort (ρ = Spearman correlation coefficient). Each region is illustrated in red on a coronal slice of the cerebellum (Y-coordinate provided) to the right of the relevant scatterplots.

above, activation in this region did not differ significantly between the FRDA and control cohorts. This observation raises the possibility that dysfunction may characterize only a subset of individuals with FRDA. To test this hypothesis, a *post-hoc* median split of the FRDA cohort was specified based on the clinical index score (see *Methods: Behavioural Data Analysis*; Table S7). A one-way ANOVA was then run across the three groups (controls, high clinical scores, low clinical scores); [$F(2,62) = 3.56, P = 0.035$]. While neither half of the clinical group differed significantly from the control cohort, the trends in the data point toward relative *increases* in activation in the less severe group, and relative *decreases* in the more severe group (see also Table S8 for comparable comparisons between “classical” FRDA [onset < 25 yrs] and Late-Onset FRDA [onset > 25yrs]).

No associations between activation magnitudes and clinical index scores were evident in the cerebrum or in cerebello-cerebral connectivity ($|\rho|(29) = 0.03\text{--}0.26$, all $P > 0.05$).

Behavioral Correlations

Across all participants, individual response variability (SD) was positively correlated with activations in right lobule VI ($\rho(63) = 0.29, P = 0.022$) and lobule VIIb ($\rho(63) = 0.26, P = 0.041$), in line with the putative role of these regions in smoothing cognitive processes. As illustrated in Figure 5A, while this effect was comparable in both groups within lobule

VI (CON: $\rho(34) = 0.25$; FRDA: $\rho(29) = 0.32$), the association was specific to the control group in lobule VIIb (CON: $\rho(34) = 0.44$; FRDA: $\rho(29) = 0.02$).

In the cerebral cortex, correlations between task performance and rIPFC activations were only found in controls for both SD (CON: $\rho(34) = 0.43, P = 0.011$; FRDA: $\rho(29) = 0.01, P = 0.95$) and RT (CON: $\rho(34) = 0.40, P = 0.02$; FRDA: $\rho(29) = 0.15, P = 0.44$; Fig. 5B). This effect was comparable in the anterior insula for SD (CON: $\rho(34) = 0.39, P = 0.02$; FRDA: $\rho(29) = 0.08, P = 0.67$) and trending to significance for RT in controls (CON: $\rho(34) = 0.32, P = 0.07$; FRDA: $\rho(29) = 0.22, P = 0.25$). As such, increased brain activation in these regions was associated with more variable and/or poorer task performance, but only in controls.

Similarly, greater task-related cerebello-insular dynamic connectivity in the left hemisphere was also associated with greater behavioral variance (SD) in controls ($\rho(34) = 0.40, P = 0.02$), but not in FRDA ($\rho(29) = -0.15, P = 0.43$; Fig. 5C). These results together point to a loss of normal brain-behavior correspondence in individuals with FRDA in the same regions and connections that also show between-group magnitude differences.

DISCUSSION

In this study, we report a convergence of abnormalities in both localized brain function and inter-regional functional connectivity in cerebello-cerebral brain circuits underlying higher-order cognition in individuals with FRDA. This convergence was particularly evident in the anterior insula and rostrolateral prefrontal cortex of the cerebrum, the ventrolateral thalamus, and lobule VI of the cerebellum. Dysconnectivity between these regions was observed as both a generalized property of neural network function, as well as a task-specific abnormality in dynamic connectivity. In individuals with FRDA, clinical metrics were predictive of function in the cerebellum, while dissociations between brain function and task performance were observed with respect to cerebral function and cerebello-cerebral connectivity. Taken together, these findings point to network-level changes in brain systems supporting cognition in individuals with FRDA.

Within the cerebellar cortex, deficits in the neural response to cognitive manipulations were observed in areas previously implicated in working memory, executive functions, and language processing, including lobule VI, neighboring regions of crus I, and lobule VIIb [E, et al., 2014; Stoodley, et al., 2012]. This finding is consistent with previous reports of deficits in working memory and higher-order cognition in FRDA [Fielding, et al., 2010; Hocking, et al., 2014; Klopper, et al., 2011; Mantovan, et al., 2006; Nieto, et al., 2012]. Notably, dysfunction also extended into more prototypical motor regions of lobule V and VI [Stoodley and Schmahmann, 2009], in line with reported disruptions at the interface between motor and cognitive functions [Corben, et al., 2010; Corben, et al., 2011b; Corben, et al., 2011c].

Figure 5.

Behavioural Correlations. Linear associations between task performance and (A) cerebellar activations in lobules VI (left) and VIIb (right), (B) cerebral activations in rostralateral prefrontal cortex (left) and anterior insula (right), and (C) cerebello-

cerebral dynamic connectivity in controls (blue) and individuals with FRDA (red). SD = response time standard deviation (2-back > 0-back); RT = response time magnitude (2-back > 0-back); ρ = Spearman correlation coefficient.

These observations support neural dysfunction within the cerebellum that extends beyond primary pathology in the dentate nuclei [Koeppen, et al., 2011a], and influences systems implicated in both motor and nonmotor functions.

Assessments of function in the dentate nuclei revealed a more varied pattern of dysfunction. Less severe disease states were associated with relative hyperactivity compared with controls, potentially reflecting either a decrease in inhibitory input from dysfunctional regions of the cerebellar cortex, or alternatively, local mechanisms of compensatory function. Conversely, greater clinical severity was characterized by reduced neural function, perhaps the consequence of more profound cell loss in the dentate. As such, the functional consequences of dentate nuclear atrophy underlying FRDA are not entirely straightforward.

The pattern of observed functional changes in prefrontal and insular cerebral cortices is broadly consistent with previous fMRI studies of response inhibition [Georgiou-Karistianis, et al., 2012] and motor execution [Akhlaghi, et al., 2012] in individuals with FRDA. However, beyond simple dysfunction, between-group differences were driven by a pattern of activation deficits in “task-positive” regions of

the rostralateral prefrontal cortex, anterior insula, and frontal operculum, alongside more pronounced deactivation in “task-negative” areas of the midinsula and parietal operculum. These “task-positive” brain regions correspond to components of the canonical “salience” network of the brain [Buckner, et al., 2011; Habas, et al., 2009; Yeo, et al., 2011], which is implicated in the process of identifying behaviorally-relevant contextual information and maintaining attentional task-sets during goal-directed cognition [Cocchi, et al., 2013; Dosenbach, et al., 2007; Uddin, 2015]. Conversely, these “task-negative” regions are putatively responsible for interoceptive and somatosensory processes [Cauda, et al., 2012; Kurth, et al., 2010; Taylor, et al., 2009]. As such, pronounced down-regulation of internalizing operations may serve to compensate for deficits in up-regulating externalizing functions (c.f., [Bosch, et al., 2010; Kochan, et al., 2010]).

Group activation differences were clearly lateralized to the left cerebral (and right cerebellar) hemispheres. Within the prefrontal cortex, research suggests that language-based cognition preferentially relies on the left cortex, while spatial-based cognition is lateralized to the right

[Stephan, et al., 2003]. While beyond the scope of this study to confirm, two interpretations emerge: first, the demands of this verbal working memory task selectively exceeded the capacity of the left, but not right, hemisphere processes in individuals with FRDA; or alternatively, cognitive deficits underlying FRDA may be weighted toward left-lateralized processes alongside other language deficits that characterize the disorder.

It is notable that alongside observed functional changes in “salience” regions observed in this study, task-related brain function in executive control systems, including lobule VII/VIIIb of the cerebellum [Stoodley and Schmahmann, 2009], dorsal and caudal areas of the lateral prefrontal cortex, and the intraparietal sulcus [Harding, et al., 2015] were relatively spared in individuals with FRDA. Dysfunction in FRDA may, therefore, be particularly weighted to task-set maintenance and the detection of behaviorally-relevant information in the environment, as opposed to abnormalities in top-down control or executive planning processes *per se* [Dosenbach, et al., 2007].

The localized neural changes observed within these cerebellar and cerebral regions were paralleled by changes in the functional interactions that define their integration into a large-scale brain network. The observation of generalized (static) cerebello-cerebral functional dysconnectivity is consistent with decreases in the underlying white-matter anatomical substrates that link the cerebellum to the cerebrum [Akhlaghi, et al., 2011; Clemm von Hohenberg, et al., 2013; Corben, et al., 2014; Della Nave, et al., 2008b; Della Nave, et al., 2011; Pagani, et al., 2010; Rizzo, et al., 2011; Vieira Karuta, et al., 2015; Zalesky, et al., 2014]. On top of this foundation of generalized dysconnectivity, additional deficits of task-related dynamics may provide a link between functional abnormalities observed in the cerebellum and the cerebrum. However, recent evidence also suggests that prefronto-cerebellar decoupling may be associated with more efficacious or well-learned cognitive states [Hirose, et al., 2014]. As such, the lack of observed dynamics may suggest that individuals with FRDA required ongoing compensatory fronto-cerebellar coupling to perform the task on par with the controls.

Established pathophysiological and neuroanatomical evidence in FRDA indicates that, within the brain, pathology is largely based in the cerebellum [Della Nave, et al., 2008a; Koeppen, et al., 2011a]. In support, our findings showed that individual clinical status was specifically associated with cerebellar, but not cerebral, dysfunction. Additionally, correlations between behavioural performance and both cerebral function and fronto-cerebellar connectivity were observed in controls, but not in individuals with FRDA. That is, in addition to group-level quantitative changes in brain function, these brain systems were also not responsive to individual differences in cognitive load. Taken together, while primary pathology occurs in the cerebellum, the propensity for cognitive dysfunction in FRDA likely results from neural changes that manifest downstream of this pathology.

It is important to recognize that the neurofunctional group differences reported in this work occur alongside matched behavioural performance. This situation likely reflects the action of compensation mechanisms (see above) and/or residual capacity in the cognitive system [Fornito, et al., 2015]. Control-matched behavior allows brain differences to be interpreted independent of behavioural confounds induced by disease or medication-related effects [Price, et al., 2006]; however, generalizations to states of dysfunction must be made with caution. Additionally, a number of individuals in this FRDA cohort met criteria for late-onset FRDA (8 of 29), defined by illness onset after the age of 25 years (coinciding with putative completion of neurodevelopment). We report preliminary evidence that these individuals may have less severe biological abnormalities as compared to “classical” FRDA [Koeppen, et al., 2011b]. However, we also note that in some cases the relationship between onset age and these biological indices is linear across the entire sample, particularly in cerebellar regions. As such, further research is required to determine whether there are categorical/qualitative differences between “late-onset” and “classical” FRDA over-and-above the commonly reported continuous relationship between onset age and disease severity [Nachbauer, et al., 2014].

Several limitations of the current work are notable. First, covariance-based analyses of functional connectivity are not indicative of direct, mono-synaptic interconnectivity [O’Reilly, et al., 2012]. Moreover, although PPIs infer directional source-to-target relationships (i.e., cerebellar contributions to neural activity in frontal systems, and not *vice-versa*), causality cannot be conclusively determined from these findings [Gerchen, et al., 2014]. Therefore, while the current results support a disruption in large-scale functional integration, the role of specific efferent/afferent fibers or targeted synapses within the cerebello-cerebral circuit cannot be inferred. Future use of effective connectivity [Friston, 2011] or computational modeling techniques [Alstott, et al., 2009] would be useful in this regard. Second, functional connectivity was not assessed from the dentate nuclei, where principal pathology is known to manifest in FRDA. Atrophy of the dentate nuclei, alongside a lack of robust individual-level functional activations, prevented selection of functionally consistent seed regions across all individuals in the FRDA cohort. Future investigations of dentate connectivity using more powerful task designs and higher-field MRI are therefore indicated [c.f., Stefanescu, et al., 2015]. Finally, while the pattern of cross-sectional results presented herein provides insight into disease-related dysfunction, this study is insensitive to the dynamic processes that may parallel and underpin progressive brain atrophy and functional decline over time. Future longitudinal studies will be necessary to address these questions.

In summary, this work provides evidence that FRDA is characterized by neurofunctional changes in fronto-cerebellar pathways underlying higher-order cognition. These changes reflect a pattern of primary dysfunction

within the cerebellum, with downstream alterations potentially reflecting mechanisms of both dysfunction and compensation. Taken together with a burgeoning body of associated behavioral and neuroimaging findings, this work conceptualizes FRDA as a brain disorder that extends beyond the confines of the cerebellum.

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