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Longitudinal Study of Cognitive Functioning in Friedreich's Ataxia

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Abstract

Objective: Friedreich's ataxia (FRDA) is the most common hereditary ataxia. It is a neurodegenerative disorder, characterized by progressive ataxia. FRDA is also associated with cognitive impairments. To date, the evolution of cognitive functioning is unknown. Our aim was to investigate the changes in the cognitive functioning of FRDA patients over an average eight-year timeframe. In addition, we aimed to study the relationship between cognitive changes and clinical variables. **Methods:** Twenty-nine FRDA patients who had been part of the sample of a previous study participated in the present study. The mean average time between the two assessments was 8.24 years. The participants completed an extensive battery of neuropsychological tests chosen to examine cognitive functioning in various cognitive domains: processing speed, attention, working memory, executive functions, verbal and visual memory, visuoperceptive and visuospatial skills, visuoconstructive functions and language. **Results:** At follow-up, cerebellar symptoms had worsened, and patients presented greater disability. Differences between baseline and follow-up were observed in motor and cognitive reaction times, several trials of the Stroop test, semantic fluency, and block designs. No other cognitive changes were observed. Deterioration in simple cognitive reactions times and block designs performance correlated with the progression of cerebellar symptoms. **Conclusions:** Our study has demonstrated for the first time that patients with FRDA experience a significant decline over time in several cognitive domains. Specifically, after an eight-year period, FRDA patients worsened in processing speed, fluency, and visuoconstructive skills. This progression is unlikely to be due to greater motor or speech impairment.

Keywords: Friedreich's ataxia, Longitudinal study, Cognition, Neuropsychology, Cerebellum

INTRODUCTION

Friedreich's ataxia (FRDA), the most common hereditary ataxia, is an autosomal recessive disorder, clinically characterized by slowly progressive ataxia, dysarthria, areflexia, and loss of vibratory and proprioceptive sensation (Harding, 1984). Disease onset typically occurs in late childhood or early adolescence. The estimated prevalence of FRDA is 2–4/100,000 (Vankan, 2013). The majority of FRDA cases are linked to an expansion mutation of GAA repeats within the frataxin gene which encodes the mitochondrial protein frataxin (Campuzano et al., 1996). The physiological consequences of frataxin deficiency are a severe disruption of iron–sulfur cluster biosynthesis, mitochondrial iron overload coupled to cellular iron dysregulation and an increased sensitivity to oxidative stress (Schmucker & Puccio, 2010). A relation between the number of GAA repeats in the shorter allele and the age at onset and disease severity has been demonstrated (i.e. Dürr et al., 1996; Filla et al., 1996; Koeppen, 1998; Tsou et al., 2011).

Neurodegeneration in FRDA extends to the central and peripheral nervous system. The neuropathological changes of FRDA fundamentally involve the dorsal root ganglia, the spinal cord, with degeneration of posterior columns and spinocerebellar tracts, and the dentate nucleus of the cerebellum (i.e. Koeppen, 2011; Koeppen & Mazurkiewicz, 2013; Koeppen, Ramirez, Becker, & Mazurkiewicz, 2016; Koeppen et al., 2009). Magnetic resonance imaging (MRI) studies have demonstrated cerebellar atrophy and have confirmed the reduction of both the dentate nucleus and the superior cerebellar peduncles observed in post-mortem studies (i.e. Cocozza et al., 2020, França et al., 2009; Pagani et al., 2010; Solbach et al., 2014)

In addition, macro and micro-structural damage have been also observed in many supratentorial cerebral regions, but the available data still do not form a clear pattern (i.e. Rezende et al., 2016, 2017; Zalesky et al., 2014). Functional imaging studies have also shown various cerebellar and cerebral

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abnormalities. Thus, for example, during motor-sensory tasks, Ginestroni et al. (2012) observed areas of decreased activation (i.e. sensory-motor cortex, lobules V, VI and VIII of right cerebellum, thalamus, and prefrontal cortex), and areas of increased activation (i.e. parietal and precentral cortex, anterior cingulate, and striatum). This mixed pattern of results is frequently observed and have been related with compensatory and degenerative mechanism, although their interpretation is still unclear (Selvadurai, Harding, Corben, & Georgiou-Karistianis, 2016).

Neuropsychological studies suggest that FRDA is also associated with cognitive impairments. The most consistent findings are the slowing of cognitive processing speed and the impairment in executive tasks, whereas data about the state of other cognitive functions are more contradictory (Corben et al., 2011, 2017; De Nóbrega, Nieto, Barroso, & Montón, 2007; Nachbauer et al., 2014; Sayah, et al., 2018). In previous studies, our research group reported a reduced processing speed and impairments in conceptual thinking, verbal fluency, verbal learning, visuoperceptive and visuoconstructive functions, and action naming. These results pointed to a dysfunction of prefrontal and temporo-parietal system (Nieto, Correia, De Nóbrega, Montón, & Barroso, 2013; Nieto et al., 2012).

Longitudinal studies of degenerative diseases are important to know disease progression and to provide prognostic information. However, there are only a few longitudinal studies on the progression of FRDA. In general, they have shown that clinical progression is faster than other cerebellar ataxias and that early onset of the disease and a higher number of GAA triplet repeats is associated with a faster progression (Fahey, Corben, Collins, Churchyard, & Delatycki, 2007; Patel et al., 2016; Reetz et al., 2016). To the best of our knowledge, no study has been conducted on the cognitive evolution of FRDA patients. Therefore, it is currently unknown whether there is also a progression in cognitive impairment and what variables might be associated with it. Thus, the aim of the present study was to investigate the changes in the cognitive functioning of FRDA patients over an average eight-year timeframe. In addition, we aimed to study the relationship between cognitive changes and clinical variables.

METHODS

Participants

FRDA patients who had been part of the sample of a previous study (Nieto et al., 2012) participated in the present study. At baseline, 36 patients were consecutively recruited from the ataxia units of three Spanish hospitals: Ntra. Sra. Candelaria University Hospital (S/C de Tenerife), Marqués de Valdecillas Hospital (Cantabria), and La Paz Hospital (Madrid). All participants fulfilled the diagnostic criteria for FRDA and presented the molecular genotype of FRDA. Detailed information of the sample can be found in our previous work (Nieto et al., 2012). 81% of patients in the initial sample participated in the present study (two patients died, five patients declined to participate, and the level of deterioration of one patient impeded their evaluation). Therefore, 29 patients were re-examined at follow-up. All patients underwent a neurological examination. No patient had developed other neurological diseases. MRI was performed on every patient and MR images were clinically assessed by an experienced neuro-radiologist. Neither cerebral atrophy nor focal lesions were observed.

Table 1. Demographic and clinical characteristics of patients at baseline and follow-up

	Baseline Mean (*SD*)	Follow-up Mean (*SD*)
Age	34.52 (12.73)	43.28 (12.90)
Education (years)	12.59 (4.19)	12.66 (4.30)
Sex	14/15	
Information subtest	15.52 (6.16)	16.20 (5.12)
MMSE	28.76 (1.4)	28.14 (1.70)
Age of onset	19.31 (9.90)	
GAA1/GAA2	512 (256.53)/704 (315.48)	
Disease duration	15.21 (8.50)	23.55 (8.40)

The mean average time between the two assessments was 8.24 years (range from 7 years 6 months to 9 years 10 months). The mean duration of illness was 15.21 ($SD = 8.50$) at baseline and 23.55 ($SD = 8.40$) at the follow-up. Mean age at disease onset was 19.31 years ($SD = 9.90$) (Table 1).

Considering the mean age of the participants (34.5 years at baseline and 43.2 years at follow-up), the changes observed between the two assessments are unlikely to be due to aging. Nevertheless, in order to confirm that the possible deterioration observed was not an effect of ageing, two control groups were included in the study. Given the impossibility of conducting a second examination of the controls who participated in the initial study, a control group was formed which matched the demographic characteristics of the patients at baseline, as well as a second group matched to the characteristics of the patients at follow-up. These two groups were evaluated with the tasks in which significant differences were obtained between the two evaluations of the sample of patients. The participants in the control samples were free of neurological disease, drug addiction, and psychiatric illness histories. Patients and their corresponding control groups did not differ with respect to age, level of education, Mini-Mental State Examination (MMSE) score, and Information score (WAIS-III).

MATERIALS

The Rankin Disability Scale (Nobile–Orazio, Baldini, & Barbieri, 1988) and the Clinical Rating Scale (CRS) modified from Appollonio, Grafman, & Schwartz (1993) were used to quantify disease. The CRS assesses seven cerebellar signs (dysarthria, limb tone, postural tremor, upper- and lower-limb

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Table 2. Neuropsychological test administered grouped by cognitive domains

Global screening
Mini-Mental State Examination (MMSE)
Information Subtest (WAIS-III)
Beck's Depression Inventory (BDI)
Reaction Time, Attention, and Working Memory (WM)
Simple Reaction Time (Pc-Vienna System)
Choice Reaction Time (Pc-Vienna System)
Continuous Performance Test (CPT-IP)
Stroop Word and Color Test
Digit Span (WMS-III)
Spatial Span (WMS-III)
Executive functions
Wisconsin Card Sorting Test (WCST)
Similarities Subtest (WAIS-III)
Verbal fluency (FAS, animals, and actions)
Memory and learning
Logical Memory (WMS-III)
California Verbal Learning Test (CVLT)
10/36 Spatial Recall Test (10/36 SRT)
Visuoperceptive, visuospatial, and visuoconstructive abilities
Judgment Line Orientation Test (JLOT)
Facial Recognition Test (FRT)
Block Design (WAIS-III)
Language
Noun and action naming
Anaphoras

ataxia, standing balance, and gait ataxia) and abnormalities in ocular movements. Total scores on this scale ranged from 0 to 32; the higher the score, the worser the dysfunction. Depression was assessed by the Beck Depression Inventory (BDI) (Beck et al.,1961).

The participants completed an extensive battery of neuropsychological tests chosen to examine cognitive functioning in various cognitive domains (Table 2). Tests were selected in such a way that no or only limited movement had to be performed by the patient. Additionally, motor control tasks and statistical methods were used to control for the effect of worsening in motor coordination deficits, psychomotor slowness, and dysarthria. A detailed description of the materials and procedures may be found elsewhere (Nieto et al., 2012).

Simple and choice reaction time tasks of the Reaction Unit/Vienna System (RT) were used (Schuhfried, 1992). This system permits the dissociation of decision and motor times. Decision time is a cognitive measure of information processing speed. A computerized version of the Continuous Performance Test (CPT)—identical pairs paradigm (Erlenmeyer-Kimling & Cornblatt, 1992)—was administered in order to measure sustained attention. The total number of correct responses were obtained. Selective attention was assessed with the Stroop Color and Word Test (Golden, 1978). Working memory was tested with Digit span and Spatial span (forward and backward; Wechsler Memory Scale, WMS-III) (Wechsler, 1997a).

Executive functions were assessed with the Wisconsin Card Sorting Test (WCST) (Heaton, 1981), Similarities subtest of the WAIS-III (Wechsler, 1997b), and three verbal fluency tasks (phonemic, semantic, and action fluency (Benton, Hamsher, & Sivan, 1989; Piatt, Fields, Paolo, & Tröster, 1999). Verbal memory was tested with the Spanish adaptation of the California Verbal Learning Test (Benedet & Alejandre, 1998; Delis, Kramer, Kaplan, & Ober, 1987) and the Logical Memory subtest (WMS-III) (Wechsler, 1997a). Visual memory was tested with a modified 10/36 Spatial Recall Test (10/36) (Rao, Leo, Bernardin, & Unverzagt, 1991), a memory task for spatial locations that does not require good motor control.

Visuoperceptive and visuospatial skills were assessed with the Facial Recognition Test (FRT) (Benton, Hamsher, Varney, & Spreen, 1983) and an abbreviated version of the Judgment Line Orientation Test (Benton et al., 1983). A modified Block Design subtest of the WAIS-III was used (Wechsler, 1997b) for the assessment of visuoconstructive skills. In order to take into account, the motor deficits of patients, subjects were allowed to work on each problem for one extra minute, and the number of correct blocks was recorded without any kind of speed credits. Additionally, a motor baseline task was administered, and execution time was recorded. This task was equivalent to the original Block Design Test in terms of motor demand but had minimal perceptive and planning requirements. This test consisted of making two designs, one four-block design, and one nine-block design, with all the red faces of the blocks at the top. Regarding language, naming was assessed with a visual confrontation task consisting of 40 stimuli representing elements (noun naming) and 20 stimuli depicting action scenes (action naming). Nouns and actions were paired by word frequency (Benton et al., 1989) and nominal agreement (Piatt et al., 1999). Comprehension was tested with an anaphora task.

Procedure and Data Analysis

Neuropsychological tasks were administered by an experienced clinical neuropsychologist over two sessions. Neuropsychological examination was always performed at the corresponding hospital. Scales used to quantify neurological impairment were administered by neurologists from ataxia units. All participants gave their informed consent. The procedure complied with the Declaration of Helsinki for medical research involving human subjects and was approved by the ethics committee of the University of La Laguna.

Differences in participant performance between baseline and follow-up were studied using repeated measure analysis of variance. Multivariate analysis with Time (baseline vs. follow-up) and task as variables were conducted when the tasks included different conditions or modalities. In some cases, the analyses were complemented by ANCOVA. The Bonferroni test correction was applied to control type-I errors. The effect sizes of comparisons in ANOVA and

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Table 3. Changes in clinical measures and cognitive performance between baseline and follow-up

	Baseline	Follow-up		
	Mean (*SD*)	Mean (*SD*)	*p*-Value	Effect size (η_p^2)
Neurological symptoms				
Rankin disability scale	2.93 (.92)	3.66 (.86)	<.001[a]	.41
Clinical cerebellar ataxia scale	16.00 (6.03)	18.38 (5.45)	.006[a]	.24
Processing speed (Pc-Vienna)			.002[a]	.36
Simple decision time (ms)	434.30 (109.19)	538.09 (202.24)		
Simple motor time (ms)	387.17 (148.17)	572.48 (334.08)		
Choice decision time (ms)	555.39 (105.76)	662.78 (234.97)		
Choice motor time (ms)	428.00 (157.79)	650.74 (396.14)		
Stroop color word test			<.001[b]	.71
Word	72.58 (17.37)	59.17 (17.12)	<.001[c]	.71
Color	54.21 (11.12)	47.25 (11.96)	<.001[c]	.64
Word-Color	31.04 (8.03)	27.85 (6.01)	N.S.[c]	.14
Interference score	0.311 (6.74)	1.728 (6.72)	N.S.[c]	.54
Verbal fluency			.010[b]	.004
Phonemic (FAS)	27.21 (9.35)	27.00 (9.00)	N.S.[c]	0
Semantic (animals)	19.68 (4.41)	16.96 (4.36)	.003[c]	.3
Action	13.04 (5.51)	14.79 (7.19)	N.S.[c]	.05
Block design			.008[a]	.45
Easy designs-standard time	16.85 (.55)	15.15 (2.30)		
Complex designs-standard time	33.31 (7.71)	24.38 (10.40)		
Easy designs-extended time.	17.00 (.00)	16.77 (.59)		
Complex designs-extended time	38.77 (6.77)	29.38 (9.94)		

[a] *p*-Value for Time factor.
[b] *p*-Value for Time × Task interaction
[c] *p*-Value for Bonferroni tests conducted when the interaction Time × Task was significant.
N.S. no significant.

ANCOVA were estimated by partial eta squared (η_p^2). Correlations between variables were determined by Pearson's coefficient. A variable representing the change was calculated to study the relationship between the cognitive differences observed and the clinical parameters. For reaction time measures and neurological scales, this variable was calculated subtracting results at baseline from results at follow-up (follow-up−baseline). An equivalent variable was calculated for number of corrects responses: baseline−follow-up. Thus, higher values indicate a greater worsening in all the cases. Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS, Chicago, IL).

RESULTS

As shown in Table 3, significant differences were found between the baseline and the follow-up, both in the Rankin Disability Scale ($F^{(1,28)} = 19.538$; $p < .001$; $\eta_p^2 = .41$) and in the CRS ($F^{(1,28)} = 8.629$; $p = .006$; $\eta_p^2 = .24$). No significant differences were found in the BDI. The change in CRS scores correlated inversely with age at disease onset ($r = -.42$; $p = .02$). Disease duration or GAA repeats did not correlate with clinical progression.

The MANOVA conducted for reaction times tasks showed a significant main effect for Time ($F^{(1,22)} = 12.584$; $p = .002$; $\eta_p^2 = .36$) but no significance for the interaction Time × Task, indicating that in the follow-up there are longer reaction times than at baseline and that this worsening is similar in all tasks.

No significant difference was found between the first and second assessment in the Continuous Performance Test task. In the Stroop Color Word Test, both the Time factor and the interaction Time × Task were significant ($F^{(1,23)} = 56.416$; $p < .001$; $\eta_p^2 = .71$; $F^{(1,22)} = 12.212$; $p < .001$; $\eta_p^2 = .55$, respectively). A worsening of performance was observed at follow-up in trials 1 (Words) ($F^{(1,22)} = 56.080$; $p < .001$; $\eta_p^2 = .71$) and trial 2 (Colors) ($F^{(1,22)} = 41.569$; $p < .001$; $\eta_p^2 = .64$) but the differences in trial 3 (Color-Word) were nonsignificant. The changes in the performance in the Stroop Test could be associated with a worsening in participants' dysarthria. Therefore, an ANCOVA was performed using the change in the scores of the dysarthria item of the CRS as covariate. Nonetheless, dysarthria was not a significant covariant ($F^{(1,22)} = 2.230$; $p = .150$; $\eta_p^2 = .09$). In the case of the Stroop Interference score, no significant difference was found between the baseline and the follow-up.

Regarding verbal working memory, no significant effects were observed in Digit Forward or Backward. In the case of visual working memory, the Time × Task interaction was significant ($F^{(1,14)} = 8.151$; $p = .013$; $\eta_p^2 = .368$) but subsequent analyses did not show significant differences between baseline and follow-up. No differences between the two assessments were observed in any of the declarative memory tests.

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With regard to executive functions, the Time × Task interaction was significant in the analysis of participants' performance in Verbal Fluency tasks ($F^{(1,27)} = 5.498$; $p = .010$; $\eta_p^2 = .30$). Post-hoc analyses showed significant differences between baseline and follow-up in the Semantic Fluency task ($F^{(1,27)} = 10.970$; $p = .003$; $\eta_p^2 = .30$). ANCOVAs were performed in order to control the possible effects of the worsening of articulatory deficits or the cognitive slowness. However, neither the change in dysarthria ($F^{(1,26)} = .068$; $p = .796$; $\eta_p^2 = .003$) nor the change in reaction time were significant covariant ($F^{(1,21)} = .088$; $p = .770$; $\eta_p^2 = .004$). No differences between the two assessments were found in the Similarities subtest or in the Wisconsin Card Sorting Test with respect to visuoperceptive and visuospatial performance; no significant differences were observed in the FRT or the Judgment Line Orientation Test between baseline and follow-up. Regarding visuoconstructive skills, we grouped Block Design trials into easy and complex designs. The MANOVA conducted for Block Design trials showed a significant main effect for Time ($F^{(1,12)} = .997$; $p = .008$; $\eta_p^2 = .45$) but no significance for the interaction Time × Task × Execution Time, indicating that the score decreased in follow-up independently of the task (simple vs. complex) and the minutes allowed. The effect observed could be related with a deterioration of the motor coordination or a lower motor speed. Nonetheless, the worsening in the Control Task was not significant as a covariate ($F^{(1,10)} = .569$; $p = .841$; $\eta_p^2 = .004$).

Regarding language, no significant differences were found between baseline and follow-up in Noun or Action Naming or the Anaphora Comprehension tasks.

Correlational analyses were performed to study the relationship between cognitive changes and clinical variables. Regarding processing speed, a significant correlation was found between the change in the Simple Decision Time and the change in the CRS ($r = .533$, $p = .007$). The deterioration in Simple Motor Time correlated inversely with the age of disease onset ($r = -.531$, $p = .008$). With respect to performance in the Stroop test, we found a significant correlation between the number of GAA1 repeats and the worsening in trial 1 (Words) ($r = .516$, $p = .017$). The lower performance in complex Block designs (standard time) correlates significantly with the deterioration in the CRS ($r = .62$, $p = .024$). No other correlations were significant.

Finally, in order to determine whether the deterioration observed could be due to aging and not to the progression of the disease, the performance of the control groups in the tasks in which the patients worsened was analyzed. No deterioration was observed in any of the cases.

DISCUSSION

This study re-examined FRDA patients after a mean average of 8.24 years. As expected, the cerebellar symptoms of FRDA patients had worsened and they presented a greater disability. A greater progression of clinical symptomatology was associated with a younger age at the onset of the disease. These results are in line with available data from cross-sectional and longitudinal studies (Reetz et al., 2015, 2016). However, FRDA patients did not experience any significant changes in mood. Depression has been little explored in FRDA (Costabile et al., 2018; Da Silva et al., 2013; Nieto, Hernández-Torres, Pérez-Flores, & Montón, 2018) and has not been included in studies on the progression of this disease. Neurological worsening might be expected to contribute to an increased presence of depression symptoms, but our data do not support this notion.

The main aim of this study was to investigate cognitive changes in FRDA. Regarding processing speed, the participants showed an increase of reactions times. This increase was observed in all the tasks (simple and choice reactions) and components (motor and decision times), indicating a generalized reduction in motor and cognitive processing speed. This slowing is a consistent finding in FRDA (i.e. Corben et al., 2010; Nieto et al., 2012, 2013), and the present findings show that it is also a progressive impairment.

FRDA patients did not show changes in sustained attention, as measured with the Continuous Performance test, or selective attention, as measured by the Stroop test. In the latter task, although the interference score was not different over time, a lower performance was observed in word and color naming (Trial 1 and 2). This worsening was not related with an increase in articulatory difficulties. Therefore, this may be further evidence of the slowing of processing speed. Working memory and declarative memory remained unchanged at follow-up.

Regarding verbal fluency, we observed a worsening in the semantic task. Performance in these tasks can be affected by articulatory problems and a slowed processing speed. Analyses conducted to account for these confounding factors show that the decrease in semantic fluency cannot be attributed to a worsening of dysarthria or to a reduction of processing speed. In addition, if there was a significant influence of motor-articulatory impairment or cognitive slowness on the worsening in verbal fluency performances, then all three tasks should have been affected. The fact that there has been no deterioration in either phonemic or action fluency indicates that the observed worsening in semantic fluency cannot be attributed to a worsening of dysarthria or to a reduction in processing speed.

Impairment in verbal fluency is one consistent characteristic of the neuropsychological profile of FRDA patients. The results obtained show that this impairment is also progressive. This finding is consistent with that of the cross-sectional study carried out by the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS), which reported a progressive worsening of verbal fluency over 25 years (Reetz et al., 2015), and with the negative relationship observed between duration of disease and verbal fluency by Dogan et al. (2016). It is worth mentioning that the fluency task used in these two studies was the phonemic modality. In our study, we did not observe changes in phonemic fluency, but we did in semantic fluency. It could be possible that

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changes in phonemic need a longer time to be observed. Other executive functions assessed, such as capacity for categorization, conceptualization, and flexibility, did not diminish after eight years of progression of the disease.

Visuospatial and visuoperceptive functions skills remained unchanged, but block designs task showed a decrease at follow-up. The interpretation of visuoconstructive results in movement disorders is always complicated. Therefore, we designed an assessment procedure that included the elimination of time credit, the softening of time limitations, and a motor control task. As expected, participant's performance in the motor control task diminished in the follow-up task but the change was not a significant covariant in the analyses of blocks designs performance. Taking the above into account, the decrease observed in block designs does not seem to be due to motor slowness or motor coordination deficits. Therefore, our results indicate that there is a worsening of visuoconstructive skills. Regarding linguistic functions, no changes were observed in participants' performance in the naming or comprehension tasks.

Deterioration in simple cognitive reactions times and block designs performance correlated with the progression of cerebellar symptoms as measured by the CRS, but no other relationship between neurological and cognitive deterioration was observed. This result suggests that no parallel can be drawn between the evolution of the cognitive state and the evolution of neurological symptomatology, at least in an eight-year follow-up period. Neither the age at disease onset nor the GAA repeats were relevant variables.

The main limitation of this study is the lack of neuroimaging data that allow us to establish relationships between cognitive changes and possible changes in MRI parameters. Another limitation is that we lack the data on neurological impairment provided by modern standardized scales, which limits the possibility of comparing clinical impairment with other studies. Further studies may also include some of the procedures proposed by Saccà et al. (2017) to complement the management of dysarthria or motor impairment.

In summary, our study has demonstrated for the first time that patients with FRDA experience a significant decline over time in several cognitive domains. Specifically, after an eight-year period, FRDA patients worsen in processing speed, fluency, and visuoconstructive skills. This progression is unlikely to be due to a greater articulatory impairment, an increased slowness or aging. The most prominent pathology in FRDA is the degeneration of the spinal cord and the cerebellum. Traditionally, the cerebellum was considered a neural system restricted to motor control and coordination. However, anatomical studies, functional neuroimaging studies, and studies on the effects of cerebellar damage have provided evidence that the cerebellum is involved in cognition and affect (e.g. Buckner, 2013; Manto & Mariën, 2015; Schmahmann, 2013; Strick, Dum, & Fiez, 2009). More specifically, cerebellar lesions have been related with deficits in executive functions, including verbal fluency, and visuospatial disintegration, among others (Schmahmman, 2013). The cerebello-thalamic-cortical circuit connect the cerebellum with supratentorial regions implicated in high-level processes. These pathways facilitate the incorporation of the cerebellum into the neural circuits subserving cognition and emotion. The dentate nucleus is a central node in the anatomy of cerebellar connections, relaying the majority of fibers exiting the cerebellar cortex, and the superior cerebellar peduncles are the output pathway (Guell et al., 2020). As noted, cerebellar atrophy and the reduction of both the dentate nucleus and the superior cerebellar peduncles are characteristics of FRDA. In addition, supratentorial anomalies have been reported in FRDA patients in white matter and cortical regions. Therefore, the cognitive deficit reported in FDRA may be the consequences of these abnormalities in the cerebellar-cortical system (e.g. Cocozza et al., 2018; Selvadurai et al., 2020; Zalesky et al., 2014). In this same line, the cognitive changes observed in this research may be related to the longitudinal microstructural changes reported in diffusion tensor imaging studies (Mascalchi et al., 2016; Rezende et al., 2016). These longitudinal changes have been observed in the superior cerebellar peduncles, the corpus callosum, and the cerebral white matter. The distribution of these changes suggests that FRDA patients present a progressive deficit in cerebellar-cerebral connectivity and this is in line with the decrease in processing speed and the deterioration of cognitive tasks that require connections between multiple cerebral regions.

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CONFLICT OF INTEREST

The authors have nothing to disclose.

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