Cognition in Friedreich Ataxia: a Neuropsychological and RS-fMRI Study

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Introduction

Several studies have evaluated cognitive impairment in Friedreich Ataxia (FRDA) reporting a modest and discordant cognitive dysfunction. Previous activation fMRI studies showed the presence of low activation patterns during motor and behavioral tasks. Unfortunately, no resting-state fMRI (RS-fMRI) analysis has been performed in FRDA. Aim of the study was to perform a thorough neuropsychological analysis and a RS-fMRI evaluation in FRDA patients

Methods

Neuropsychological Assessment

Type of test	List of tests
Global Assessment	The Montreal Cognitive Assessment
Language	Naming Nouns and Pointing
Intelligence	Raven Colored Progressive Matrices
Executive Functions	Symbol Digit Modalities Test, Attentional Matrices, Trail Making Test, Brief Stroop Test, Weigl's Sorting Test, Phonetic and Semantic Fluencies
Memory	Digit Span , 10/36 Spatial Recall Test, Rey Auditory Verbal Learning Test
Visuospatial Functions	Segment Length Discrimination, Mental Rotation

Radiology

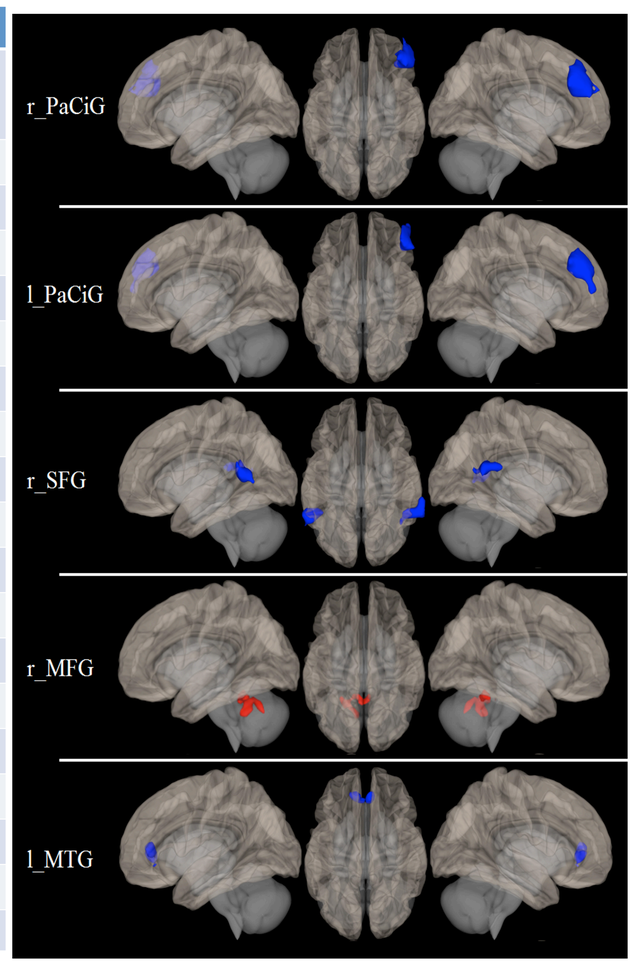
- All MRI studies were performed on the same 3 Tesla scanner.
- A seed-based RS-fMRI approach (areas related to executive and cognitive functions) that might have been compromised in patients.
- Functional connectivity maps were entered in a second level analysis to test for differences between the two groups.
- Differences were considered significant for $P < 0.0011$, corrected for multiple comparisons.

Results

Neuropsychology

Function	Test	FRDA (SD)	Controls (SD)	Effect Size	*p*
Global Assessment	**MOCA**	22.3 (3.6)	26.2 (2.3)	0.33	**<0.001**
Language	**Pointing Names**	23.9 (0.3)	24 (0.2)	0.02	0.301
	Naming Nouns	13.9 (1.3)	14.2 (1.2)	0.01	0.568
Intelligence	**RCPM**	29.6 (6.3)	33 (5.4)	0.08	0.050
Memory	**Digit Span**	7 (4.4)	6.5 (1.1)	0.01	0.454
	1036 immediate	18.5 (6.6)	22.9 (3.8)	0.12	**0.017**
	1036 recall	6.5 (2.4)	8.2 (1.8)	0.13	**0.012**
	RAVLT immediate	40.8 (12.6)	47.5 (9.4)	0.08	0.052
	RAVLT recall	9.3 (3.9)	10.5 (3.4)	0.03	0.250
Visuospatial	**SLD**	26.9 (2.2)	28.5 (1.7)	0.18	**0.003**
	Mental Rotation	93.3 (15.9)	105.8 (4.7)	0.15	**0.008**
Executive	**SDMT**	35.8 (10)	57.3 (13.6)	0.50	**<0.001**
	Attentional Matrices	50.5 (8.7)	55.5 (3.2)	0.05	0.118
	TMT-A	67 (68.9)	29.8 (8.8)	0.27	**<0.001**
	TMT-B	127.3 (57.7)	73.2 (24.2)	0.33	**<0.001**
	Brief Stroop Test	50.1 (20.3)	26.9 (7.4)	0.44	**<0.001**
	Weigl's Sorting Test	12.6 (2.2)	13.6 (1.5)	0.04	0.197
	Semantic Fluency	18.5 (5.8)	23.7 (4.9)	0.25	**0.001**
	Phonemic Fluency	27.5 (11.7)	41.3 (8.8)	0.31	**<0.001**

RS-fMRI



Areas of increased connectivity are shown in blue, areas of reduced connectivity are shown in red.

r_PaCiG = right paracingulate gyrus;
l_PaCiG = left paracingulate gyrus;
r_SFG = right superior frontal gyrus;
r_MFG = right medial frontal gyrus;
l_MTG = left middle temporal gyrus.

Seed	Clusters	Difference	p
r_PaCiG	r_MFG	HC<FRDA	$1*10^{-8}$
l_PaCiG	r_MFG	HC<FRDA	$1*10^{-6}$
r_SFG	R and l angular gyri	HC<FRDA	$1*10^{-4}$
r_MFG	Lobule 6 and vermis	HC>FRDA	$1*10^{-4}$
l_MTG	Cingulate gyrus	HC<FRDA	0.0011

Clinical and RS-fMRI correlations

	r_MFG cluster (r_PaCiG seed)	r_MFG cluster (l_PaCiG seed)	Angular gyri (r_SFG seed)	Cerebellar cluster (r_MFG seed)	Cingulate cluster (l_MTG seed)
MOCA	n.s.	n.s.	n.s.	n.s.	n.s.
Pointing Names	n.s.	n.s.	n.s.	n.s.	n.s.
Naming Nouns	n.s.	n.s.	n.s.	n.s.	n.s.
RCPM	n.s.	n.s.	n.s.	n.s.	n.s.
Digit Span	P=0.009*	n.s.	P=0.047*,a	n.s.	n.s.
1036 immediate	n.s.	n.s.	n.s.	n.s.	n.s.
1036 recall	n.s.	n.s.	n.s.	n.s.	n.s.
RAVLT immediate	n.s.	n.s.	n.s.	n.s.	n.s.
RAVLT recall	n.s.	n.s.	n.s.	n.s.	n.s.
SLD	n.s.	n.s.	n.s.	n.s.	n.s.
Mental Rotation	P=0.014*	n.s.	n.s.	n.s.	n.s.
SDMT	n.s.	n.s.	n.s.	n.s.	n.s.
Attentional Matrix	P=0.037*	n.s.	n.s.	n.s.	n.s.
TMT-A	n.s.	n.s.	P=0.007#,a	n.s.	n.s.
TMT-B	P=0.006#	n.s.	P=0.024#,a	n.s.	n.s.
Brief Stroop Test	P=0.027#	P=0.036#	P=0.007#,a P=0.036#,b	n.s.	n.s.
Phonemic Fluency	n.s.	n.s.	n.s.	n.s.	n.s.
Semantic Fluency	n.s.	n.s.	n.s.	n.s.	n.s.

r_PaCiG = right paracingulate gyrus; l_PaCiG = left paracingulate gyrus; r_SFG = right superior frontal gyrus; r_MFG = right medial frontal gyrus; l_MTG = left middle temporal gyrus;
** = direct correlation; # = inverse correlation; a = left angular gyrus; b = right angular gyrus.*

Conclusions

- FRDA showed a higher than expected impairment of cognitive functions
- Significantly worst functioning was observed in global cognition, clear-thinking ability, non-verbal intelligence, spatial and verbal memory, visuoperception and visuospatial functions, and executive functions
- RS-fMRI showed widespread alterations of connectivity that showed a correlation with executive function test results