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Cognitive and Psychological Functioning in Fabry Disease

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Abstract

Fabry disease is an X-linked lysosomal storage disorder which can result in renal, cardiac, and cerebrovascular disease. Patients are at increased risk of stroke and neuroimaging studies note cerebrovascular pathology. This study provides a cognitive profile of a cohort of individuals with Fabry disease and investigates the impact of pain, age, renal, cardiac, and cerebrovascular functioning on cognition and psychological functioning. Seventeen Fabry patients (12 males) with ages ranging 25 to 60 years (M = 46.6+11.8), and 15 age-matched healthy controls (M = 46.2+12.7) were administered a comprehensive neuropsychological battery. Fabry males demonstrated slower speed of information processing, reduced performance on measures of executive functions (verbal generation, reasoning, problem solving, perseveration), were more likely to show clinically significant reductions, and were more likely to report symptoms of anxiety and depression. Conversely, Fabry females performed at a similar level to controls. Correlational analyses indicated a link between cognitive and clinical measures of disease severity.

Keywords: Fabry disease; Neuropsychology; Psychology; Depression; Anxiety; Cognition

Introduction

Fabry disease is an X-linked lysosomal storage disorder that is characterized by a deficiency of the lysosomal enzyme α-galactosidase A due to mutations in the *GLA* gene. Deficiency of this enzyme results in an accumulation of globotriaosylceramide and other glycosphingolipids, causing cellular dysfunction in various cell types throughout the body and resulting in progressive symptoms, including neuropathic pain, angiokeratomas, gastrointestinal, ophthalmologic, renal disease, cardiovascular dysfunction, and cerebrovascular disease (Zarate & Hopkin, 2008). Historically, the incidence of Fabry disease has been estimated as 1 in every 117,000 live births in Australian males (Meikle, Hopwood, Clague, & Carey, 1999). While this study did not report on incidence in females, the data have been extrapolated to suggest a combined incidence of 1 in 58,000 in the general Australian population (Fuller, Meikle, & Hopwood, 2006). Recent studies have, however, indicated that non-classical forms may be relatively common in some populations (Lin et al., 2009).

Due to the X-linked nature of Fabry disease, the classic phenotype occurs in hemizygous males who typically have <1% of normal α-galactosidase A activity (Mehta et al., 2004). Despite often presenting with normal levels of α-galactosidase A, females may still experience clinical manifestations of Fabry disease, though these are typically milder symptoms and present with a later age of onset (Deegan et al., 2006).

Cerebral manifestations can occur in Fabry disease, resulting in an increase in disease burden and lower quality of life (Crutchfield et al., 1998). The risk of stroke is greatly increased, especially at younger ages than the general population (Sims, Politei, Banikazemi, & Lee, 2009). Structural alterations in the brain have been observed, particularly in the posterior circulation, with findings of significant enlargement of the basilar artery as well as the larger vessels of the circle of Willis (Fellgiebel, et al., 2009; Mitsias & Levine, 1996; Moore, Kaneski, Askari, & Schiffmann, 2007). White matter changes are also a feature in Fabry

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disease, with radiological studies of Fabry disease patients documenting a high burden of white matter lesions (WML), particularly in periventricular areas, the internal capsule and deep white matter, with WML typically accumulating with age (Crutchfield et al., 1998; Fellgiebel et al., 2005).

That there exists such significant cerebrovascular pathology in patients with Fabry disease raises questions regarding cognitive functioning in this population. The literature addressing neuropsychological performance in cerebrovascular conditions, such as stroke and/or transient ischemic attacks (TIAs), suggests that the prominent features include slowed speed of information processing and executive dysfunction, the latter most frequently characterized by reductions on tasks assessing abstract reasoning, mental flexibility, and working memory (Debette & Markus, 2010; Sachdev et al., 2004). However, impairments in other areas of cognition, including visual and verbal memory, language, praxis, and attention, have also been observed, as would be expected given variabilities within and between samples in site and mechanism of the cerebrovascular disturbance (Reed et al., 2007; Sachdev et al., 2004). The available literature on cognitive functioning in Fabry disease is limited, as might be expected given the rare nature of this disorder. There are three published group studies investigating this issue: Segal and colleagues (2010) explored psychiatric and cognitive issues in 16 children and adults with Fabry disease, noting poorer speed of information processing and reductions on computerized tasks of executive functioning and attention (IntegNeuro computerized battery). In contrast, Schermuly and colleagues (2011) reported that the only deficit in cognition observed in their sample of 25 adult patients with Fabry disease was for sustained attention, compared with 20 healthy control participants. Significant differences between Fabry and control groups were also noted for executive functions (Wisconsin Card Sorting Test, Total Errors score), though this difference did not remain significant after controlling for depression severity. An investigation of 17 adults with Fabry disease was conducted at the Royal Melbourne Hospital by Low and colleagues (2007) utilized brief cognitive screening measures (Mini-Mental State Examination, MMSE, and the Neuropsychiatry Unit Cognitive Screen, NUCOG). Participants were not found to be significantly different from controls on the total scores of these measures. Interestingly, differences were found in the NUCOG domain scores whereby the Fabry disease patients scored significantly *higher* than controls on attention and significantly *lower* than controls on language.

Given the psychosocial and medical stressors present for individuals with Fabry disease as well as the impact this disorder has on quality of life, it is not surprising that Fabry disease patients are considered at higher risk for developing psychological conditions such as depression and anxiety disorders (Cole et al., 2007; Hoffmann, 2006). Two well-designed surveys of large samples of Fabry disease patients have been published to date (Cole et al., 2007; Crosbie, 2006), both of which have reported depression as prevalent in Fabry disease. In their investigation of 25 patients with Fabry disease, Schermuly and colleagues (2011) found depression to be common, with 60% of the sample showing elevated symptoms of depression on the Hamilton Rating Scale for Depression. Similarly, Segal and colleagues (2010) reported that out of their sample of 16 Fabry disease patients, 4 adults had been diagnosed with major depressive disorder.

Despite studies highlighting cerebrovascular involvement, limited attention has been given to cognitive outcomes in Fabry disease. Methodologies in these studies have been varied, ranging from brief cognitive screens (Low et al., 2007) to neuropsychological assessment (Schermuly et al., 2011; Segal et al., 2010), with inclusion of a mixed sample of adults and children (Segal et al., 2010). Therefore, the aim of the present study was to characterize cognitive functioning in a cohort of Fabry disease patients using comprehensive and well-validated neuropsychological measures, as well as to examine potential relationships between cognition and clinical characteristics of Fabry disease.

As the cognitive profile of Fabry disease was expected to reflect the cerebrovascular issues and subcortical white matter changes that may present in the disease, the cognitive functions of speed of information processing and executive skills were hypothesized to be those most likely to be impacted. Given the literature to date on disease burden across genders, it was predicted that cognitive impacts on males with Fabry disease would be greater and present at an earlier age than for females. Furthermore, the presence of symptoms of depression, stress, and anxiety in the Fabry disease cohort were expected given the high prevalence of mood disorders in Fabry patients reported in the literature (Cole et al., 2007; Hoffmann, 2006).

Methods

Participants

Eighteen of 50 individuals known to the Department of Medical Genetics at Westmead Hospital with a diagnosis of Fabry disease confirmed through blood assays of α-galactosidase A levels and/or molecular genetic analysis agreed to participate in the study. One participant was excluded from the analysis due to co-morbid diagnosis of Behçet's disease. The final study cohort therefore comprised 17 participants (12 males and 5 females) with ages ranging from 25 to 60 years (mean age of 46.6, *SD* of 11.8 years). A sample of 15 age-matched healthy participants (nine males and six females) was recruited from the community as part of this study to serve as controls for neuropsychological measures. Recruitment and assessment was conducted over a 2-year period. Demographic information of the study cohort is presented in Table 1. This prospective study was approved by the

Human Research Ethics Committee (Westmead Campus) and Macquarie University Ethics Committee. All participants provided written informed consent prior to commencing the study.

Neuropsychological Measures

All participants completed standardized and extensive neuropsychological testing assessing ten cognitive domains, including intellectual functioning (Test of Premorbid Functioning, Wechsler Adult Intelligence Scale, Fourth Edition; WAIS-IV; Wechsler, Coalson, & Raiford, 2008), memory (California Verbal Learning Test, Second Edition; CVLT-II; Delis, Kramer, Kaplan, & Ober,, 2000; Wechsler Memory Scale, Fourth Edition; Wechsler, Holdnack, & Drozdick, 2009), immediate attention and working memory (WAIS-IV Digit Span), visuospatial (WAIS-IV Block Design), speed of information processing (WAIS-IV Coding and Symbol Search), language (WAIS-IV Vocabulary, Boston Naming Test; Tombaugh & Hubley, 1997), reasoning skills (WAIS-IV Similarities, Matrix Reasoning and Visual Puzzles), verbal fluency (Verbal Fluency; Tombaugh, Kozak, & Rees, 1999), and problem solving (Wisconsin Card Sorting Test [WCST]; Heaton, Chelune, Talley Kay, & Curtis, 1993). Participants also completed self-report questionnaires assessing psychological functioning (Depression, Anxiety and Stress scale, DASS-21; Lovibond & Lovibond, 1995) and pain levels (Brief Pain Inventory, BPI; Cleeland & Ryan, 1994). Raw scores on neuropsychological tasks were transformed into standard scores based on published normative data appropriate to the participant's gender, age, and level of education.

Clinical Measures

Information on clinical characteristics and symptom severity was obtained from review of medical records, including the Mainz Severity Scoring Index (MSSI) (developed by Whybra et al., 2004 specifically for Fabry disease to quantify the severity of disease symptoms). The maximum total score for this scale is 76, and it is divided into four sub-sections that address general (scored out of 18), neurological (20), cardiovascular (20), and renal symptoms (18). Staging of chronic kidney disease (CKD) was represented by the measured glomerular filtration rate (GFR) ranging from Stage 1 (normal kidney function: GFR $>$ 90), Stage 2 (mildly reduced kidney function: GFR $=$ 60–90), Stage 3 (moderately reduced kidney function: GFR $=$ 30–60), Stage 4 (severely reduced kidney function: GFR $=$ 15–30) to Stage 5 (end-stage renal failure: GFR $\leq$ 15).

Statistical Analysis

Demographic and cognitive data were examined using independent samples *t*-tests, with the Bonferroni correction applied to control for family wise error rate. Data that did not meet the assumptions of normality or homogeneity of variance were analyzed

Table 1. Demographic and clinical characteristics of study participants

	Fabry disease			Controls		
	Males, $n = 12$	Females, $n = 5$	Total, $n = 17$	Males, $n = 9$	Females, $n = 6$	Total, $n = 15$
Age	44.3 (12.3)	52.4 (9.2)	46.6 (11.8)	40.8 (13.1)	54.3 (6.3)	46.2 (12.7)
Years of education	12.2 (2.9)	13 (3)	12.4 (2.8)	14.22 (2.6)	13.5 (3.02)	13.9 (2.7)
Age diagnosed	38 (11.3)	45.2 (17.3)	40.6 (13.5)			
Receiving ERT	66.7%	20%	52.9%			
CVA/TIA	33%	0%	0%			
CKD stage	2.6 (1.4)[a]	1 (0)	2.1 (1.4)			
MSSI						
Total	22.7 (12.4)[a]	3.8 (3.9)	17.1 (13.7)			
General	3.6 (2.3)	0.6 (0.9)	2.7 (2.4)			
Neurological	4.7 (3.9)[a]	1.6 (3.4)	3.7 (3.9)			
Cardiovascular	8.2 (7.1)[a]	0 (0)	5.7 (7.1)			
Renal	6.3 (5.9)	1.6 (2.2)	4.9 (5.5)			
BPI						
Severity	2 (1.6)[a]	1.5 (1.6)	1.8 (1.6)	0.4 (1.0)	0.9 (1.1)	0.6 (1.1)
Intensity	2.6 (3.1)[a]	1.0 (1.8)	2.1 (2.8)	0.5 (1.1)	1.0 (1.6)	0.7 (1.3)

Notes: Means (*SD*) are reported.
ERT = enzyme replacement therapy; CVA = cerebrovascular accident; TIA = transient ischemic attack; MSSI = Mainz Severity Scoring Index; CKD = chronic kidney disease; BPI = Brief Pain Inventory.
[a]Statistical significance at $p < .05$.

using the Mann–Whitney *U* test (WCST categories completed, DASS-21 measures, CKD, BPI). For analyses of cognitive differences between groups, test scores were converted to *z*-scores and averaged to create one score to represent the 10 cognitive domains examined. As gender was of interest for these cognitive domains, two sets of analyses using independent samples *t*-tests with a Bonferroni correction of $p < .005$ were performed comparing first, males in the Fabry and control groups and secondly, females in the Fabry and control groups. Frequencies of impairment across groups were examined using Fisher's exact test. Further analyses using Pearson correlations (or Spearman's correlations in the cases of non-normally distributed measures) were conducted to examine the relationship between clinical characteristics, psychological state, and neuropsychological performance within the Fabry group. Statistical analysis was performed using IBM SPSS Statistics version 20.0.

Results

Demographic and Clinical Characteristics

No significant differences were observed between patients with Fabry disease that participated in the present study and those who did not in terms of age ($t_{36} = 1.4; p = .16$); however, there were significantly more female than male non-participants ($\chi^2 = 5.8, p = .01$). Statistical comparison of the Fabry disease cohort and the controls confirmed that the groups did not differ in terms of age ($t_{30} = -0.1; p = .92$), gender ($t_{30} = -0.27; p = .79$) or years of education ($t_{30} = 1.55; p = .13$). Within the Fabry cohort, there were no significant differences between males and females in terms of age ($t_{15} = 0.68; p = .51$), years of education ($t_{15} = 0.62; p = .55$), or age at diagnosis ($t_{15} = 0.95; p = .36$). With regard to clinical characteristics, males exhibited more severe symptoms of Fabry disease than females, as reflected by their higher staging of CKD ($U = 15; p = .04$), greater number of cerebrovascular events and higher total MSSI scores ($t_{15} = -2.96; p = .01$). More specifically, males scored worse on subscales of neurological ($U = 10.5; p = .02$) and cardiovascular functioning ($U = 10.5; p = .01$), though no statistically significant differences were seen for general symptoms ($U = 17; p = .1$) or on the renal subscale ($U = 12.5; p = .2$). Eight of the male Fabry participants were undergoing regular ERT, compared with only one of the females. None of the participants within the Fabry group reported experiencing visual impairment as a result of ophthalmologic symptoms.

As can be seen in Table 2, genotypes within the Fabry cohort varied greatly. No differences between Fabry males and females on BPI severity or intensity were observed. However, the Fabry group did score higher than the control group on both BPI measures (severity: $U = 63; p = .01$; intensity: $U = 74; p = .04$). Investigation of gender effects for BPI revealed that Fabry males scored higher than control males (severity: $U = 16.5; p = .006$; intensity: $U = 23; p = .02$), while Fabry females and control females had similar scores. None of the participants were prescribed antidepressant or anxiolytic medications. Fatigue was not reported by any participant during assessment.

Differences in Cognition Between Groups

Means, *SD*, and ranges of neuropsychological test results for each group are presented in Table 3. Significant differences were found between male Fabry participants and male controls on general intellectual functioning ($t_{19} = 3.4; p = .003$; 95% CI = 0.47, 1.93), speed of information processing ($t_{19} = 3.8$; $p = .001$; 95% CI = 0.53, 1.87), reasoning ($t_{19} = 3.3$; $p = .004$; 95% CI =

Table 2. Frequencies of genotype presentations of Fabry participants

Genotype	Fabry disease		
	Males, $n = 12$	Females, $n = 5$	Total, $n = 17$
p.N215S	2	1	3
c.931DELC	1	1	2
prop.Y365X	2		2
c.988DELC		1	1
g.IVS4+861C>T			1
p.M187I		1	1
p.N298K	1		1
p.A156T	1		1
p.C223Y	1		1
p.Q111X	1		1
p.R220X	1		1
Pending	1	1	2

0.31, 1.42), verbal fluency ($t_{19} = 3.7$; $p = .002$; 95% CI = 0.52, 1.85), and problem solving/perseveration ($t_{19} = 3.3$; $p = .003$; 95% CI = 0.61, 2.67). No differences were found between males in each group on immediate attention, memory, language, visuospatial, or working memory. No differences were found between females of each group in any of the cognitive domains.

To determine the clinical implications of these findings, neuropsychological test performance was examined in the context of the Heaton and colleagues (2004) system of tests score classification, which presents the following criteria for levels of impaired performance: mild (scores ranging between the 7th and 15th percentile), mild to moderate (2nd to 6th percentile), moderate (1st

Table 3. Neuropsychological test performance of study participants

Neuropsychological measures	Fabry disease				Controls			
	Males		Females		Males		Females	
	M (*SD*)	Range	*M* (*SD*)	Range	*M* (*SD*)	Range	*M* (*SD*)	Range
Premorbid								
Test of premorbid functioning[a]	102 (9.4)	79–122	104 (15.5)	88–125	109.3 (16.03)	82–126	107.8 (14.9)	84–124
General intellectual								
Full scale IQ[a]	94.9 (13.1)	75–121	109 (15.3)	94–130	113 (10.9)	98–135	116.8 (10.4)	100–129
Verbal comprehension (VCI)[a]	97.7 (14.8)	70–134	107.6 (13.8)	95–125	115.8 (12.2)	95–130	110.5 (11.9)	87–118
Perceptual reasoning (PRI[a])	97.3 (11.6)	82–115	106 (15.2)	88–127	111.3 (13.4)	92–142	121.3 (10.3)	107–131
Information processing								
Processing speed (PSI)[a]	90.9 (14.5)	65–122	110.2 (15.3)	94–134	103.9 (11.1)	86–120	108.2 (6.01)	100–114
Immediate attention								
Digits forward[b]	9.2 (1.8)	7–12	10.4 (3.2)	6–14	10.9 (3.3)	7–18	10.3 (3.01)	7–16
CVLT-II first learning trial[c]	−0.5 (1.4)	−2.5–2.5	−0.1 (1.02)	−1–1.5	−0.27 (0.9)	−1.5–1	0.42 (1.2)	−1.0–2.0
Memory								
Auditory Memory Index[a]	104 (13.9)	84–131	111.2 (14.8)	91–130	108.2 (10.7)	88–124	116.2 (9.4)	101–128
Visual Memory Index[a]	98.3 (16.8)	73–134	93.8 (4.7)	86–98	106.2 (10.4)	93–121	109.2 (9.9)	98–125
Immediate Memory Index[a]	100.7 (18.3)	67–133	103 (8.6)	94–115	108.6 (9.3)	96–125	114 (7.1)	107–123
Delayed Memory Index[a]	101.9 (15.9)	82–137	103.2 (8.9)	92–114	109.7 (9.5)	100–126	114.5 (10.3)	100–128
CVLT-II total verbal learning[c]	0.5 (1.5)	−1.1–2.8	1 (0.5)	0.4–1.7	1 (1)	−0.3–2.4	0.3 (0.6)	−0.3–1.2
CVLT-II short delay free recall[c]	0.1 (0.9)	−1–2	0.6 (0.4)	0–1	0.6 (0.5)	0–1.5	0.9 (0.8)	0–2.0
CVLT-II short delay cued recall[c]	0.3 (0.7)	−1.5–1.5	0.3 (1.2)	−1.5–1.5	0.5 (0.6)	−0.5–1.5	0.6 (0.9)	−1.05–1.5
CVLT-II long delay free recall[c]	0.3 (0.7)	−1–1.5	0.4 (0.9)	−1–1.5	0.5 (0.6)	0–1.5	0.6 (0.9)	−0.5–1.5
CVLT-II long delay cued recall[c]	0.2 (0.8)	−1–1.5	0.4 (0.8)	−0.5–1.5	0.3 (0.7)	−1–1.5	0.7 (0.9)	−1.0–1.5
CVLT-II recognition hits[d]	15 (1.2)	12–16	14.8 (1.3)	13–16	14.9 (1.2)	13–16	15.8 (0.4)	15–16
CVLT-II recognition false positives[d]	2.3 (3.1)	0–10	0.2 (0.4)	0–1	0.8 (1.1)	0–3	0.2 (0.4)	0–1
Language								
Boston Naming Test[d]	57.5 (2.6)	52–60	58.6 (3.1)	53–60	59 (1.3)	57–60	59 (1.6)	56–60
WAIS-IV vocabulary[b]	10.2 (3.5)	4–19	11.6 (2.8)	9–16	13.2 (2.6)	8–16	12.7 (3.2)	7–16
Visuospatial								
WAIS-IV block design[b]	10.6 (2.5)	6–14	11.2 (3.3)	8–15	11.8 (3.1)	9–19	13.5 (1.7)	11–16
Working memory								
Digits backward[b]	8.7 (1.6)	7–13	12 (3.5)	9–18	10.1 (2.9)	6–15	10.2 (2.4)	8–14
Digits sequencing[b]	9.7 (3.1)	5–15	12 (3.5)	7–12	12.2 (2.3)	9–17	11.5 (0.8)	11–13
Reasoning skills (executive)								
WAIS-IV similarities[b]	9 (2.1)	6–14	11 (2.8)	9–15	11 (2.4)	8–15	10.8 (1.9)	8–13
WAIS-IV matrix reasoning[b]	9.2 (2.2)	6–12	10.2 (2.7)	7–14	11.9 (2.7)	8–16	13.5 (2.8)	10–17
WAIS-IV visual puzzles[b]	9.3 (2.6)	6–13	11.8 (2.6)	9–15	12.4 (3.6)	9–19	14.7 (1.2)	13–16
Verbal fluency (executive)								
Letter fluency[c]	−1 (0.9)	−2.1–1.5	0.2 (0.6)	−0.7–0.7	0.2 (0.4)	−0.3–0.9	0.5 (0.9)	−0.5–1.9
Semantic fluency[c]	−0.7 (1.1)	−2.8–0.5	0.1 (0.8)	−0.9–1.4	0.8 (0.6)	0.05–1.9	0.9 (0.9)	−4.2–7.9
Problem solving/perseveration (executive)								
WCST categories[d]	5.25 (1.2)	3–6	6 (0)	6	6 (0)	6	6 (0)	6
WCST perseverative errors[a]	98 (19.5)	76–129	103.6 (6.8)	97–115	122.67 (14.4)	104–145	110.5 (17.5)	95–140

Notes: CVLT-II = California Verbal Learning Test, Second Edition; WAIS-IV = Wechsler Adult Intelligence Scale, Fourth Edition; WCST = Wisconsin Card Sorting Test.

[a]Standard scores ($M = 100$, $SD = 15$).

[b]Scaled scores ($M = 10$, $SD = 3$).

[c]z-scores ($M = 0$, $SD = 1$).

[d]Raw scores.

percentile), and severe (below the 1st percentile). The frequency of test scores falling below the 15th percentile was compared across groups within each cognitive domain. As seen in Table 4, a greater proportion of male Fabry participants scored below the 15th percentile than females with Fabry disease and controls on tests of processing speed (Fisher's $p = .04$), verbal fluency (Fisher's $p = .001$), and problem solving/perseveration (Fisher's $p = .02$). Of the Fabry males, 19% performed in the mildly impaired range, 7% in the mild to moderately impaired range, and 3% in the moderately impaired range.

Differences in Psychological Functioning Between Groups

Results from the DASS-21 are presented in Table 5 for Fabry and control participants. While no significant differences were seen between the overall Fabry and control groups on DASS-21 measures (depression: $U = 80.5, p = .07$; anxiety: $U = 77.5, p = .06$: stress: $U = 114, p = .61$), there was a significant difference between Fabry males and control males on anxiety scores ($U = 23.5, p = .03$). Differences between male groups for depression scores approached significance ($U = 27, p = .05$) but stress did not ($U = 42.5, p = .41$). There were no differences observed between Fabry and control females.

The majority of study participants scored within the normal range on the DASS-21 measure of depressive, anxiety, and stress symptoms. However, 8%–17% of Fabry males scored within the mild-to-moderate ranges on these measures, compared with 11% of male controls. Also, Fabry males alone reported extremely severe levels of depression and anxiety, with two males having reported a history of suicidal ideation.

The Effect of Clinical Variables on Cognitive and Psychological Performance

Not surprisingly, given that calculation of MSSI involves consideration of renal and vascular functioning, total MSSI score was strongly correlated with CKD ($r_s = .87, p = .00$) and history of CVA/TIA ($r = .59, p = .01$). Age did not correlate with measures of disease severity. Correlational analyses of cognitive and clinical variables revealed history of CVA/TIA and the MSSI neurological subscale were strongly and negatively correlated with processing speed (CVA: $r = -.61$, $p = .009$; neuro: $r_s = -.74$, $p = .00$) and similarities ($r = -.49$, $p = .04$; $r_s = -.54$, $p = .01$). CKD correlated negatively with processing speed ($r_s = -.53$, $p = .005$), while both CKD and MSSI renal correlated with letter fluency (CKD: $r_s = -.51$, $p = .003$; renal: $r_s = -.5, p = .02$). Age was only correlated with matrix reasoning ($r = -.52, p = .03$).

Table 4. Percentage of participants scoring below the 15th percentile on tests of each cognitive domain and associated Pearson χ^2 test results

Cognitive domain	Fabry disease		Controls	
	Males, $n = 12$	Females, $n = 5$	Total, $n = 15$	Fishers p-value
General intellectual	2	0	0	.13
Processing speed	3	0	0	.04[a]
Immediate attention	4	1	1	.12
Working memory	0	0	1	.62
Memory	1	0	0	.37
Language	1	1	1	.62
VisuoSpatial	1	0	0	.37
Executive				
Reasoning	2	0	0	.13
Verbal fluency	6	0	0	.001[a]
Problem Solving/perseveration	5	0	1	.02[a]

Notes: [a]Statistical significance at $p < .05$.

Table 5. Results on the DASS-21 for study participants

DASS-21:	Fabry disease			Controls		
	Males, $n = 12$	Females, $n = 5$	Total, $n = 17$	Males, $n = 9$	Females, $n = 6$	Total, $n = 15$
Depression	9 (8.5)[a]	2 (2.5)	6.9 (7.8)	2.7 (3.5)	2 (2.5)	2.4 (3.1)
Anxiety	7.5 (6.1)[b]	1.8 (1.5)	5.8 (5.8)	2.9 (2.8)	2.3 (2.9)	2.7 (2.8)
Stress	9 (5.8)	8 (13.6)	8.7 (8.3)	7.3 (7.9)	6 (4)	6.8 (6.5)

Notes: Means (*SD*) are reported.
[a]Approaches significance between Fabry males and control males at $p < .05$.
[b]Statistical significance between Fabry males and control males at $p < .05$.

Measures from the DASS-21 were not correlated with the cognitive measures presented here. However, there was a strong positive correlation between neurological symptoms (history of CVA/TIA and MSSI neuro subscale) and depression ($r = .69$, $p = .002$) and anxiety ($r = .71$, $p = .001$). Strong positive correlations were also observed between BPI measures and psychological functioning, as seen in Table 6.

Discussion

Consistent with expectations, males with Fabry disease demonstrated slower speed of information processing and reduced performance on measures of executive functions (including verbal fluency, reasoning, problem solving, and perseveration) when compared with age-matched healthy male controls. Fabry males were more likely to show clinically significant reductions on these tasks, though most demonstrated a mildly reduced performance (scores ranging from 7th to 15th percentiles). General intellectual functioning was also found to be reduced for Fabry males, consistent with the loading of processing speed and reasoning tasks on the FSIQ index. Such findings are in line with previous reports of reductions in speed of information processing and executive skills in a mixed cohort of 16 Fabry disease patients assessed by Segal and colleagues (2010). In addition, only mild reductions in sustained attention processes were found by Schermuly and colleagues (2011), which was not a cognitive construct measured in the current study.

For all the cognitive domains addressed in the present study, females with Fabry disease generally performed within normal limits on neuropsychological tests and at a similar level to healthy age-matched female controls. This is a novel finding, as differences in cognitive performance between hemizygous males and heterozygous females have not been systematically addressed in the literature. However, the relatively small sample of females included in the present research limits the generality of these gender effects.

With regard to psychological functioning, males with Fabry disease in the present study were more likely to report symptoms of anxiety and depression than females or healthy controls. Psychological distress is an important consideration when investigating cognitive functioning, as symptoms of depression, anxiety, and stress can impact performance on neuropsychological tasks (Castaneda, Tuulio-Henriksson, Marttunen, Suvisaari, & Lönnqvist, 2008). Indeed, Schermuly and colleagues (2011) found that even though executive functions in their German cohort of Fabry disease patients were reduced compared with healthy controls, that was not the case after controlling for depression severity, leading the authors to suggest that there was more of an association between depressive symptoms and executive dysfunction rather than only Fabry disease symptoms impacting on executive processes. In the present sample of patients with Fabry disease, such a marked impact of psychological distress on cognition was not observed, as symptoms of depression, anxiety, and stress were not significantly correlated with cognitive functions. Rather,

Table 6. Correlation matrix of processing speed, executive functioning, DASS-21 scores, and clinical variables for Fabry disease cohort

	Age	MSSI total	MSSI general	MSSI neuro[a]	MSSI cardiac[a]	MSSI renal[a]	CKD[a]	CVA/TIA	BPI severity[a]	BPI intensity[a]
General intellectual										
WAIS-IV FSIQ	−0.04	−0.54[b]	−0.53[b]	−0.77[b]	−0.45	−0.17	−0.44	−0.57[b]	−0.32	−0.28
Processing speed										
WAIS-IV PSI	−0.02	−0.58[b]	−0.54[b]	−0.74[b]	−0.44	−0.35	−0.53[b]	−0.61[b]	−0.17	−0.24
Reasoning										
Similarities	0.07	−0.52[b]	−0.58[b]	−0.54[b]	−0.21	−0.14	−0.43	−0.49[b]	−0.22	−0.31
Matrix reasoning	−0.52[b]	−0.44	−0.14	−0.42	−0.64[b]	−0.19	−0.24	−0.55[b]	−0.11	−0.02
Visual puzzles	−0.01	−0.45	−0.27	−0.17	−0.52[b]	−0.23	−0.44	−0.37	−0.25	−0.25
Verbal fluency										
Letter	0.25	−0.50[b]	−0.58[b]	−0.41	−0.67[b]	−0.55[b]	−0.51[b]	−0.25	−0.18	−0.26
Semantic	−0.19	−0.43	−0.06	−0.10	−0.19	−0.03	−0.27	−0.21	−0.07	0.13
Problem solving/perseveration										
WCST categories[a]	−0.04	−0.21	0.08	−0.19	−0.30	−0.01	−0.05	−0.32	−0.24	−0.23
WCST PE	−0.12	−0.23	0.03	−0.03	−0.22	−0.16	−0.29	−0.37	−0.21	−0.23
DASS-21										
Depression	0.18	0.46	0.23	0.50[b]	0.32	0.25	0.24	0.69[b]	0.41[b]	0.39[b]
Anxiety	−0.03	0.52[b]	0.36	0.56[b]	0.38	0.35	0.36	0.71[b]	0.61[b]	0.61[b]
Stress	−0.16	0.11	0.22	0.20	0.26	0.22	0.18	0.33	0.38[b]	0.45[b]

Notes: Pearson's or Spearman's correlation coefficients are reported.
All others presented are Pearson's correlation coefficients.
[a]Spearman's correlation coefficient.
[b]Statistical significance at $p < .05$.

psychological distress scores were significantly correlated with the self-reported pain levels within the Fabry group—which, along with disease severity, were highest for Fabry males. While anxiety has not been specifically investigated in Fabry disease, studies outlining clinical diagnoses of major depressive disorder (Segal et al., 2010) and surveys highlighting higher rates of self-report depressive symptoms in Fabry disease patients (Cole et al., 2007; Crosbie, 2006) suggest that psychological distress is an important consideration for ongoing Fabry disease management. Previous research has also found the presence of neuropathic pain to impact on emotional functioning (Gold et al., 2002).

The association between clinical features of Fabry disease and cognition has received little attention in the literature. Certainly, cognitive impairments seen in some case studies of Fabry disease patients have been attributed to the specific impact of glycosphingolipid accumulation on cerebral circulation (Mendez, Stanley, Medel, Li, & Tedesco, 1997; Okeda & Nisihara, 2008). However, unlike CADASIL (another genetic disorder presenting with early onset cerebrovascular pathology), Fabry disease is multi-systemic—where an interplay of cerebrovascular, renal and cardiac symptoms reflect a broad baseline heterogeneity, and so the overall cognitive impact may not be due simply to white matter changes as seen on MRI. While Segal and colleagues (2010) report that patients demonstrating cognitive impairments presented with an average of 2.4 clinical symptoms, compared with 1.8 symptoms present for those who scores on cognitive tasks were in the normal range, the significance of this difference on identification of symptoms was not addressed. In this study, correlational analysis revealed that cerebrovascular integrity in particular was strongly associated with cognitive variables, with notable reductions in speed of information processing and reasoning skills observed for those with a history of CVA/TIA. Additionally, worsening renal and cardiac function was also associated with lower scores on executive measures.

Worsening disease burden has been linked with increasing age in a number of studies, with negative correlations of age with renal and cardiac function, cerebrovascular disease, and quality of life being noted for both males (Fellgiebel et al., 2005; Germain, 2010; Miners, Holmes, Sherr, Jenkinson, & MacDermot, 2002) and females (Deegan et al., 2006; Fellgiebel et al., 2005). In a large-scale population study utilizing FOS data from of 617 males and 655 females with Fabry disease, the average total MSSI score was found to increase with each decade (Hughes, Ramaswami, Barba Romero, & Deegan, 2010). However, the present study did not find a significant association between age and measures of disease severity, or between age and cognitive functions. It is noted that any prediction of disease progression over the lifespan in the current study was restricted by the small sample size and cross-sectional analyses, highlighting the need for well-designed longitudinal studies. To better account for the impacts of pain and reactive mood disorders on cognition, future work might also consider comparison with a neurologically sparing chronic disease group.

In summary, Fabry disease is a rare disorder, which is reflected in the small sample size of the current study recruited over a 2-year period. Results of the study suggest that neuropsychological findings in this group of Fabry disease participants is consistent with a cerebrovascular profile, with males more likely to present with reductions in speed of information processing, executive functions and psychological distress. In addition, correlational findings suggested a relationship between cognition and clinical measures of disease severity that incorporate aspects of disease presentation, such as severity of cardiac, cerebrovascular, and renal functioning. Given that cognitive weaknesses and psychological distress can impact considerably on quality of life and vocational outcomes (Mehta et al., 2009), a better understanding of cognitive and psychological issues in Fabry disease patients has important implications for health service planning, evaluation of therapeutic treatments (such as ERT) and clinical management of this population.

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Conflict of Interest

None declared.

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