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Cognitive function impacts gait, functional mobility and falls in Fragile X-Associated Tremor/Ataxia Syndrome

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Abstract

Background: Executive function and information processing speed deficits occur in fragile X premutation carriers (PMC) with and without fragile X-associated tremor/ataxia syndrome (FXTAS). Gait is negatively impacted by cognitive deficits in many patient populations resulting in increased morbidity and falls but these relationships have not been studied in FXTAS.

Research question: We sought to investigate the associations between executive function and information processing speed and gait, turning and falls in PMC with and without FXTAS compared to healthy controls.

Methods: Global cognition and the cognitive domains of information processing speed, attention, response inhibition, working memory and verbal fluency were tested with a neuropsychological test battery in 18 PMC with FXTAS, 15 PMC without FXTAS, and 27 controls. An inertial sensor based instrumented Timed Up and Go was employed to test gait, turns and functional mobility.

Results: Lower information processing speed was significantly associated with shorter stride length, reflecting slower gait speed, in PMC with FXTAS ($p = 0.0006$) but not PMC without FXTAS or controls. Lower response inhibition was also significantly associated with slower turn-to-sit times in PMC with FXTAS ($p = 0.034$) but not in those without FXTAS or controls. Lower information processing speed ($p = 0.012$) and working memory ($p = 0.004$), were significantly correlated with a greater number of self-reported falls in the past year in FXTAS participants.

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Significance: This is the first study demonstrating that worse executive function and slower information processing speed is associated with reduced gait speed and functional mobility, as well as with a higher retrospective fall history in participants with FXTAS. This information may be important in the design of cognitive and motor interventions for this neurodegenerative disorder.

Keywords

Fragile X-associated tremor/ataxia syndrome (FXTAS); Cognitive function; Gait and Functional Mobility; Instrumented Timed Up and Go (i-TUG); Fall risk

Introduction

Fragile X-associated tremor/ataxia syndrome (FXTAS) is a progressive neurodegenerative disease that affects a significant number of carriers of a 'premutation' size (55–200) CGG repeat expansion in the 5' untranslated region of the *fragile X mental retardation 1 (FMR1)* gene on the X chromosome [1]. FXTAS patients may present with a combination of clinical symptoms including cerebellar gait ataxia, balance problems, tremor, parkinsonism, peripheral neuropathy and cognitive deficits. *FMR1* premutation carrier (PMC) men are more frequently and severely affected with FXTAS than PMC women due to the protective presence of a normal *FMR1* allele on the second X chromosome [1–4] and perhaps random X inactivation in women [5–7].

The primary cognitive phenotype in FXTAS is frontal executive dysfunction [8]. Deficits reported in men with FXTAS include impairments in working memory, attentional control, response inhibition and self-regulation, verbal fluency, and information processing speed. These cognitive deficits may progress to dementia in advanced disease stages. Women with FXTAS may also have deficits in executive function including areas of response inhibition and performance monitoring [8,9]. The executive dysfunction phenotype in FXTAS is similar to the "cerebellar cognitive affective syndrome" observed in other cerebellar disorders [10]. This phenomenon has been associated with neurodegeneration in cerebrotocerebellar circuits that connect with the prefrontal cortex [11]. Deficits in executive function have also been reported in PMC without FXTAS [8,12–14]. Whether or not these are prodromal markers for FXTAS or a neurodevelopmental effect of the premutation remains to be determined.

Gait performance is negatively impacted by cognitive deficits in many patient populations, increasing fall risk, morbidity and mortality [15]. While cognitive function and gait have been explored separately in PMC with and without FXTAS, the only study examining associations between executive function and gait were conducted in women PMC without FXTAS [16]. However, no studies have examined the impact of cognition on gait function in PMC men and women with FXTAS. This is especially important because PMC men have a higher risk for developing FXTAS and may have greater disease severity than women, and women with FXTAS have been understudied. Therefore, we examined the association between cognitive function and gait in PMC men and women with and without FXTAS compared to controls. We also correlated cognitive function and gait scores with the number

of self-reported falls occurring in the past year. We hypothesized that lower executive function and processing speed would be associated with worse gait performance, especially in PMC with FXTAS, perhaps highlighting previously identified deficits in frontal cortico-cerebellar networks [17] and associated gait neural centers. Specifically, abnormalities in the genu and middle cerebellar peduncles (MCP) were found to correlate with worse executive function in PMC with and without FXTAS. Information gleaned from the present study is needed to determine fall risk in patients with FXTAS and may lead to the development of therapies tailored to their individual cognitive and gait deficits.

METHODS

Participants

PMC were recruited from the Fragile X-Associated Disorders Program at Rush University Medical Center (RUMC). Most were identified through family members of children with fragile X syndrome. A detailed medical history, neurological examination and MRI, when available, were used to diagnose FXTAS according to clinical and radiological criteria [18]. Inclusion criteria were 1) *FMRI* CGG repeat size of 55–200 (for PMC participants) and < 41 repeats on both alleles for control participants, given that some individuals in the gray zone (41–54 repeats) may have neurological signs [19], 2) the ability to perform a 7 meter Timed Up and Go (TUG) test three times, and 3) be 50 years of age or older. Exclusion criteria were 1) lower extremity orthopedic surgery within the past year, 2) additional neurological or musculoskeletal disorder that could potentially cause gait and balance problems, or 3) inability to follow directions for the testing protocol. All participants signed an informed consent approved by the Institutional Review Board at RUMC.

Gait testing

Quantitative gait and mobility analysis was performed using the APDM Mobility Lab™ inertial sensor system (APDM™; Oregon) [20]. The well validated and reliable instrumented 7 meter TUG(i-TUG) was performed three times as previously described [21] and the mean value for each gait parameter was calculated. i-TUG variables are known to correlate with disease severity in other movement disorders including Parkinson Disease (PD) [22]. Variables were selected from key gait domains thought to reflect independent features of neural locomotor control in older adults [23], including 1) gait speed (stride length and velocity), 2) rhythm (cadence), 3) gait variability (stride length and cadence variability), and 4) gait cycle phase (percentage of gait cycle spent in swing and double limb support). Intra-individual gait variability was determined by the coefficient of variation (standard deviation/mean × 100). Gait symmetry was not assessed because we previously found that it was not abnormal in patients with FXTAS [21]. A movement transition domain consisting of sit to stand, turn, turn-to-sit duration and number of steps to turn was created to assess the impact of cognition on these important functional mobility tasks.

Neuropsychological and clinical rating scale assessments

Cognitive function was measured with detailed neuropsychological assessments, assessing the domains of executive function, processing speed, verbal fluency as well as global cognition. The oral version of the Symbol Digit Modalities test (SDMT) was used to

measure information processing speed, working memory and attention [24]. This version was chosen instead of the written version to prevent potential tremor or limb ataxia from affecting subject performance. The Behavioral Dyscontrol Scale II (BDS-II) was used to measure attention and response inhibition [25]. The Controlled Oral Word Association test [26] was used to measure verbal fluency and the digit span forwards (DSF) and backwards (DSB) from the Wechsler Adult Intelligence Scale (WAIS III) was used to measure short term auditory and working memory, respectively [27]. The Montreal Cognitive Assessment (MoCA) was administered to determine global cognition and to screen for mild cognitive impairment (MCI) and dementia [28]. The FXTAS rating scale (FXTAS-RS), which rates tremor, postural sway, gait, parkinsonism, coordination, dystonia, speech, and oculomotor deficits, with higher scores reflecting more severe motor impairment, was administered to examine the signs and severity of FXTAS symptoms [5]. We also administered the Berg Balance Scale, a functional performance based balance scale [29], the mobility subscale of the Functional Independence Measure (FIM), an activities of daily living (ADL) and disability rating scale [30] and the Activities specific Balance Confidence scale (ABC), a self-reported scale of confidence when performing functional tasks [31]. Subjects were administered the total neuropathy score (TNS), modified to exclude nerve conduction velocity testing [32]. Testing for neuropathy is important given that it is found in a significant number of PMC with and without FXTAS [33] and may negatively affect gait performance. Subjects were also asked to self-report their number of falls within the past year.

Molecular Analysis

DNA was isolated from peripheral blood leukocytes or buccal cheek samples of participants. *FMRI* PCR with quantification of allele-specific CGG repeat length, and activation ratio (AR; percentage of cells with the normal *FMRI* allele on the active X chromosome) in PMC women, was performed as previously described [7].

Statistical Analysis

Demographics, cognitive measures and gait variables were compared between the three groups (controls, PMC without FXTAS and PMC with FXTAS) with ANOVA (normally distributed) or Kruskal-Wallis tests (non-normally distributed). Post-hoc pairwise comparisons were performed with Bonferroni correction or Dwass-Steel-Crichtlow-Fligner test. Sex differences were explored separately in the three groups using two way t or Mann Whitney U tests. Spearman's correlation coefficient (ρ) was used to assess the relationship between cognitive scores and i-TUG parameters separately in the three groups. Cognitive variables with significant correlations (ρ values that were < -0.5 or > 0.5) were further analyzed via linear regression analyses with i-TUG parameters as the dependent variables. Independent variables included significant cognitive variable(s) from the correlation analysis, group (control, PMC without FXTAS, PMC with FXTAS), age, sex and interaction between group and the cognitive variable (s). We hypothesized that the effects of cognition may differ in controls and PMC with and without FXTAS; therefore, the interaction effects of group and cognitive scores on the gait outcomes were explored. Given the significantly increased number of falls in PMC with FXTAS, Spearman's correlation analyses were performed to explore the association between cognitive and gait measures and the number of

falls self-reported within the past year. Given the exploratory nature of this work, correlation and regression analyses were not corrected for multiple comparisons. A $p < 0.05$ was considered significant. All statistical analyses were performed with SAS 9.3 (SAS Institute Inc., Cary NC, USA).

RESULTS

Participant Characteristics

18 PM carriers with FXTAS (9 men, 9 women), 15 without FXTAS (4 men, 11 women), and 27 controls (14 men, 13 women) underwent i-TUG and neuropsychological testing.

Demographic, cognitive function, clinical and molecular data is reported in Table 1. There were no sex differences in these variables in the three groups (except retrospective number of falls in past year was greater in men with FXTAS than women); therefore, data from men and women was grouped for analysis. As expected, participants with FXTAS were significantly older than those without FXTAS and had higher FXTAS-RS scores. They also had significantly lower SDMT ($p < 0.0001$), BDS II ($p = 0.0001$) and MoCA ($p = 0.02$) scores compared to PMC without FXTAS and controls. Digit span and COWAT scores did not differ between the three groups. None of the participants had dementia per previously established criteria [28]. The retrospective number of falls was significantly greater in the FXTAS group while BBS, FIM and ABC scores were significantly lower in PMC with FXTAS.

i-TUG results

i-TUG scores between the three groups are shown in Table 2. There were no sex differences in i-TUG variables in the three groups; therefore, data from men and women was grouped for analysis. Subjects took an average of ~100 steps over the three i-TUG trials, meeting the criteria of greater than 30 steps to accurately assess gait variability indices [34]. As previously reported [21], gait speed, rhythm and cadence variability were significantly worse in PMC with FXTAS compared to PMC carriers without FXTAS and controls. Interestingly, stride length variability was significantly greater in PMC with ($p = 0.002$) and without FXTAS ($p = 0.04$) than controls and did not differ between those with and without FXTAS. Turn and stand-to-sit duration and the number of steps to turn were significantly greater in PMC with FXTAS compared to controls and those without FXTAS.

Correlations between cognitive function scores and gait, turn and movement transition domains are shown in Table 3. In PMC with FXTAS, lower SDMT scores were significantly correlated with reduced stride length and velocity ($p = 0.003$ and 0.01), and slower sit-to-stand, turn and turn-to-sit transitions ($p = 0.003$, 0.049 , and 0.01 , respectively). See Supplementary Table 1 and 2 for separate analyses in men versus women with FXTAS, respectively. Lower BDS II scores also correlated with slower turns and turn to sit duration ($p = 0.02$ and 0.014) in the FXTAS group. Lower DSB scores were significantly correlated with shorter strides ($p = 0.04$) in the FXTAS group and in PMC without FXTAS they correlated with reduced stride velocity ($p = 0.046$) and slower sit-to-stand, turn and turn-to-sit transitions ($p = 0.008$, 0.015 , and 0.02 , respectively). DSF scores were correlated with turn-to-sit duration ($p = 0.04$) in PMC without FXTAS. See Supplementary Table 3 for

separate analysis in women without FXTAS; the low sample size in men without FXTAS ($n = 4$) precluded this exploratory analysis. In controls, SDMT scores were negatively correlated with stride length and cadence variability ($p = 0.001$ and 0.0001) and turn duration ($p = 0.01$). In all PMC, CGG repeat size and AR (women only) were not correlated with any gait or cognitive measures.

Multivariate linear regression analyses adjusted for age and sex showed a significant interaction effect of SDMT and BDS II scores and the groups (controls, PMC without FXTAS and PMC with FXTAS) on stride length and sit to turn duration time, respectively. Lower SDMT scores were associated with shorter stride lengths (standardized regression coefficient (b) $\pm$ SE = 0.70 ± 0.191 ; $p = 0.0006$) and BDS II scores with longer sit to turn duration time ($b \pm$ SE = -0.465 ± 0.212 ; $p = 0.034$) in PMC with FXTAS; however, this association was not found in controls. Levels of education were not included in the analysis because they were not significantly different between the groups (Table 1).

The one year retrospective number of falls was significantly correlated with lower SDMT ($p = 0.012$), and DSB scores ($p = 0.008$) in PMC with FXTAS (Figure 1). No other i-TUG or cognitive data were correlated with falls. FXTAS-RS scores ($p = 0.01$), but not BBS, FIM or Neuropathy scores, were also significantly correlated with the number of self-reported falls in the past year.

Discussion

This is the first study to our knowledge that has examined the association between information processing speed and executive function and gait, functional mobility and falls in PMC with FXTAS compared to those without FXTAS and controls. Our findings support a significant association between lower information processing speed with worse gait speed and lower response inhibition and attention with worse turn to sit performance in FXTAS. Our results are in line with prior research in PD where lower processing speed is associated with slower gait [35]. In addition, it is likely that navigating in complex environments requires good attention and response inhibition to filter out distractions. We also found that lower processing speed and working memory were significantly correlated with the number of falls reported by PMC with FXTAS within the past year. This cognitive information may be useful in identifying predictors for heightened fall risk in patients with FXTAS.

We did not find significant cognitive and gait associations in PMC without FXTAS. This is in contrast to other studies reporting that low working memory correlated with worse gait performance in PMC women without FXTAS [16]. However, this study was conducted using a dual-task (DT) cognitive interference paradigm which increased task difficulty, and perhaps uncovered deficits not present under single-task conditions. Future studies using the DT paradigm would be worthwhile to better understand the cognitive-motor interplay in patients with FXTAS. Worsening of gait performance during a cognitive task has been reported in other movement disorders including PD [36] and in the elderly with cognitive impairment [15].

It has been proposed that executive function deficits seen in FXTAS may be caused by dysfunctional frontal networks [8]. The middle cerebellar peduncles (MCP) transmit both cognitive and motor information from the frontal lobe to the cerebellum. The known degeneration in this pathway in ~60% of men and up to 13% of women with FXTAS [33,37] may underlie the association between processing speed and attentional deficits and gait deficits in FXTAS and the likelihood that the cerebellar locomotor center [38] is disrupted in FXTAS, although this has not been formally investigated. Indeed, white matter disease in the MCP was associated with lower executive function in PMC with and without FXTAS [17]. Additionally, the cortical and cerebellar atrophy seen in many FXTAS patients (ref) is likely to relate to executive dysfunction and its negative impact on gait and balance [39]. Men with FXTAS were found to have reduced inferior frontal cortical activity while performing a working memory task [40], supporting this hypothesis. Reduced functional connectivity in the superior cerebellar peduncles, previously reported in FXTAS [41], could also impair the motor and cognitive control mechanisms between the cerebellum and the frontal lobe. This is supported by the role of the cerebellum in cognition, especially by connecting with prefrontal cortical areas [42].

Our results have important ramifications for the design of interventional strategies aimed at improving both cognition and gait, turning and functional mobility in FXTAS. Identification of processing speed deficits is particularly important in FXTAS because this cognitive domain has the potential to be improved with cognitive training [43]. Moreover, a cognitive remediation program in PD participants resulted in improved turning speed [44]. DT cognitive and motor training paradigms have also been shown to improve gait and cognitive function [45] and reduce fall risk in healthy older adults and elderly fallers [46] and in patients with stroke [47] and PD [48]. Videogame-based exercise has also been shown to improve prefrontal cortex activity [49], counteract age-related decline in gait [46], and reduce fall risk in stroke survivors [50]. It has also been shown to improve DT performance in MS [51] and reduce motor symptoms in individuals with degenerative cerebellar ataxias [52]. Future intervention studies in FXTAS to determine whether cognitive training methods, DT and/or virtual reality balance and gait training improved motor function are needed.

An additional novel finding in the present study was the significantly increased stride length variability in PMC without FXTAS compared to controls which did not differ from those with FXTAS. This suggests that some “asymptomatic” carriers could be developing the ataxic phenotype which is characterized by increased gait variability [53]. This potential marker of disease onset needs to be confirmed in prospective longitudinal studies.

The strengths of our study include: 1) the use of quantitative measures to evaluate gait, turning and functional mobility that provide objective metrics of motor function, 2) a complete battery of neuropsychological tests that measure different cognitive domains, and 3) retrospective reports of falls, which have never been reported in FXTAS. Limitations include our relatively small sample size, which in our initial correlation analyses caused some variables to lose significance when only women were examined compared to the FXTAS group as a whole. In addition, we did not examine visuospatial processing and its impact on gait. The SDMT has a visuospatial component, but more specific tests such as the Benton Judgment of Line Orientation test which taps into the dorsal stream visual pathway

[54] may be interesting to examine in the future given the important role of visuospatial skills in ambulation [55] and turning [56].

Conclusions

This study provides important new information about the link between processing speed and executive function and gait and falls in FXTAS. Our findings illustrate the importance of linking quantitative gait assessments with neuropsychological tests of executive function and information processing speed to elucidate the complex interplay between cognitive and motor function and fall history in FXTAS. This information will be necessary in future prospective studies to determine the inter-relationship between cognitive and gait function and prospective fall risk in FXTAS, which to date has not been investigated.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Cognitive deficits negatively impact gait and functional mobility in FXTAS
- Slower processing speed associated with worse gait speed in subjects with FXTAS
- Lower response inhibition associated with slower turn-to-sit performance in FXTAS
- Lower working memory and processing speed correlate with falls in FXT
- This information will inform the design of cognitive/motor interventions in FXTAS

Figure 1:

Spearman's correlations between A) SDMT, B) Digit Span Backwards and C) FXTAS-RS scores and the number of self-reported falls occurring in the past year in FXTAS subjects (n=18).

Key: SDMT, Symbol Digit Modalities Test; FXTAS-RS, fragile X-associated tremor/ataxia syndrome rating scale. The SDMT and Digit Span scores were scaled to age and years of education.

Subject Characteristics

Table 1

Variable	Controls (n=27)	PMC without FXTAS (n=15)	PMC with FXTAS (n=18)
Age	63.48 ± 7.73	62.73 ± 7.12	69.06 ± 6.59 * <i>a, b</i>
Sex	14 men, 13 women	4 men, 11 women	9 men, 9 women
Height (cm)	169.93 ± 9.10	168.77 ± 8.27	169.23 ± 10.96
Weight (kg)	81.05 ± 29.49	82.30 ± 30.97	87.29 ± 38.10
BMI	26.41 ± 3.98	26.47 ± 5.98	28.2 ± 5.63
Years of Education	17.52 ± 2.12	17.53 ± 3.50	16.06 ± 2.24
FMR1 CGG repeats	30.1 ± 5.41	85.36 ± 18.05 **** <i>a</i>	91.83 ± 9.01 **** <i>a</i>
FXTAS-RS	3.0 ± 1.4	8.64 ± 3.29	36.43 ± 19.66 *** <i>a, b</i>
FXTAS Diagnosis	NA	NA	6 probable, 12 definite
FXTAS Stage	NA	NA	2.89 ± 1.02
Total Neuropathy Score	0.33 ± 0.69	2.25 ± 3.20	4.71 ± 3.31 ***** <i>a</i>
FIM mobility subscale	35.0	34.8 ± 0.414	31.13 ± 5.60 ***** <i>a, *** b</i>
One-year retrospective			
Falls (#)	0.15 ± 0.36	0.6 ± 0.97	8.17 ± 14.42 ***** <i>a, * b</i>
ABC	97.59 ± 2.70	94.62 ± 4.99	67.90 ± 18.04 ***** <i>a, ** b</i>
Berg Balance Scale	55.77 ± 0.53	55.93 ± 0.27	45.93 ± 8.41 ***** <i>a, b</i>
MoCA	28.19 ± 1.44	27.54 ± 1.66	26.12 ± 2.57 ** <i>a</i>
SDMT (ss)	107.5 ± 15.78	102.1 ± 10.63	77.72 ± 12.39 ***** <i>a, **** b</i>
BDS-II	25.67 ± 0.96	24.87 ± 1.85	23.39 ± 1.91 ***** <i>a, * b</i>
Digit Span Forward (ss)	11.0 ± 3.11	11.13 ± 2.03	10.39 ± 2.62
Digit Span Backward (ss)	11.56 ± 3.33	11.53 ± 3.38	10.89 ± 2.70
COWAT (ss)	102.7 ± 15.11	103.4 ± 11.10	91.71 ± 13.66 * <i>a</i>

Age, Body mass index (BMI), Years of education, *fragile X mental retardation 1 gene (FMR1)* CGG repeats, FXTAS rating scale (FXTAS-RS), Total Neuropathy Score, Functional Independence Measure (FIM); Number of One-year retrospective falls, Activities Balance Confidence scale (ABC), Montreal Cognitive Assessment (MoCA); Symbol Digit Modalities test (SDMT); Behavioral Dyscontrol Scale II (BDS-II); Digit Span Forward and Backward, Controlled Oral Word Association test (COWAT) values/scores were compared between controls, premutation carriers (PMC) without FXTAS and PMC with FXTAS. ss = scaled score to age and years of education. All data reported as mean ± SD.

* p < 0.05,

a Significantly different from controls;
b Significantly different from PMC without EXTAS

p< 0.0001;

p< 0.001

p< 0.01
**

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Table 2.
Descriptive i-TUG data and statistics for between group comparisons in gait and movement transition variables

i-TUG Domain Variables	Controls (n=27)	PMC without FXTAS (n=15)	PMC with FXTAS (n = 18)	Control vs. PMC without FXTAS (p)	Control vs. PMC with FXTAS (p)	PMC without FXTAS vs. PMC with FXTAS (p)
Gait Speed						
Stride length (% height)	84.29 + 3.47	84.70 + 6.76	72.67 + 9.96	0.98	<0.0001	<0.0001
Stride velocity (% height/s)	77.01 + 7.73	78.44 + 12.25	61.21 + 8.64	0.88	<0.0001	<0.0001
Gait Rhythm						
Cadence (steps/min)	109.20 + 9.79	110.50 + 12.45	98.93 + 8.25	0.91	0.004	0.00
Gait Phase Cycle						
Double limb support (%)	22.15 + 5.19	24.35 + 3.96	25.51 + 5.28	0.36	0.07	0.78
Swing (%)	38.92 + 2.60	37.82 + 1.98	36.74 + 3.48	0.44	0.03	0.51
Gait Variability						
Stride length Cov	3.2	5.6	6.8	0.04	0.002	0.59
Cadence Cov	4.2	5.2	9.56	0.30	0.0001	0.003
Movement Transitions						
Sit-to-stand duration (s)	2.24 + 0.26	2.15 + 0.39	2.33 + 0.31	0.68	0.58	0.24
Turn duration (s)	2.02 + 0.41	2.03 + 0.49	3.08 + 1.28	1.00	0.0001	0.0009
# Steps to turn	4.14 + 0.90	4.16 + 0.79	5.41 + 1.36	1.00	0.0005	0.003
Turn-to-sit duration (s)	4.07 + 0.64	3.98 + 0.83	5.21 + 1.51	0.96	0.002	0.003

i-TUG variables were compared between controls, premutation carriers (PMC) without FXTAS and PMC with FXTAS. All data reported as mean ± SD. Key: i-TUG, instrumented Timed Up and Go; CoV, coefficient of variation = SD/mean × 100; PMC, premutation carriers. Note: Stride length is reported as % of total height and stride velocity as % of total height/s

Table 3

Gait and Cognition Correlations

	SDMT	BDS II	COWAT	Digit Span Forward	Digit Span Backward	MoCA
Stride Length (m/%height)	<i>a</i> 0.06	-0.07	-0.17	-0.04	0.13	0.13
	<i>b</i> 0.19	0.12	0.45	0.35	0.38	0.37
	<i>c</i> 0.65**	0.45	0.10	-0.01	0.48*	0.22
Stride Velocity (m/%height/sec)	<i>a</i> 0.33	-0.00	-0.06	0.22	0.22	0.28
	<i>b</i> 0.10	0.25	0.16	0.41	0.52*	0.11
	<i>c</i> 0.59*	0.46*	0.22	0.09	0.18	0.11
Cadence (steps/min)	<i>a</i> 0.37	0.11	-0.03	0.28	0.18	0.27
	<i>b</i> -0.03	0.31	-0.06	0.39	0.51*	0.84
	<i>c</i> 0.14	0.04	-0.30	0.19	0.07	-0.10
Double Support (%)	<i>a</i> -0.13	-0.28	0.16	-0.36	-0.14	-0.12
	<i>b</i> -0.01	-0.30	-0.003	-0.36	-0.29	-0.09
	<i>c</i> -0.15	-0.21	0.39	-0.15	-0.12	0.08
Swing (%)	<i>a</i> 0.13	0.28	-0.16	0.36	0.14	0.12
	<i>b</i> 0.01	0.30	0.003	0.36	0.29	-0.18
	<i>c</i> 0.18	0.27	-0.39	0.16	0.17	-0.08
Stride Length (CoV)	<i>a</i> -0.60**	-0.29	-0.03	-0.23	-0.30	0.04
	<i>b</i> 0.06	0.05	0.12	0.08	0.06	-0.01
	<i>c</i> -0.45	-0.37	0.01	0.14	-0.36	-0.33
Cadence (steps/min) CoV	<i>a</i> -0.67**	-0.16	-0.25	-0.10	-0.05	-0.04
	<i>b</i> -0.15	0.08	0.29	0.09	0.06	0.12
	<i>c</i> -0.02	0.30	-0.11	0.10	0.12	-0.19
Sit to stand Duration (s)	<i>a</i> -0.18	-0.04	0.07	-0.23	-0.24	0.10

	SDMT	BDS II	COWAT	Digit Span Forward	Digit Span Backward	MoCA
Turn Duration (s)	<i>b</i> -0.37	-0.07	0.27	-0.16	-0.67*	0.30
	<i>c</i> -0.65**	-0.33	-0.33	-0.20	-0.25	-0.39
	<i>a</i> -0.38*	-0.12	0.04	-0.18	-0.08	-0.21
Number of Steps to Turn	<i>b</i> 0.10	0.02	-0.53	-0.21	-0.62*	-0.11
	<i>c</i> -0.47*	-0.53*	-0.33	-0.35	-0.32	-0.07
	<i>a</i> -0.21	-0.33	0.03	-0.19	-0.05	-0.16
Turn to Sit Duration (s)	<i>b</i> 0.35	0.30	-0.18	0.24	-0.30	0.05
	<i>c</i> -0.39	-0.43	-0.19	0.03	-0.28	-0.09
	<i>a</i> -0.09	0.002	0.13	-0.27	-0.17	-0.02
	<i>b</i> -0.22	-0.37	-0.09	-0.54*	-0.59*	-0.04
	<i>c</i> -0.58*	-0.57*	-0.24	-0.22	-0.09	-0.10

Spearman's correlations were performed between Cognitive test scores and i-TUG variables. Significant correlations are bolded. Key: Symbol Digit Modalities test (SDMT); Behavioral Dyscontrol Scale II (BDS-II); Controlled Oral Word Association test (COWAT); Montreal Cognitive Assessment (MoCA); Coefficient of Variation (CoV) = SD/mean × 100.

a = Controls,

b = Premutation carriers without FXTAS,

c = Premutation carriers with FXTAS

* $p < 0.05$,

** $p < 0.01$