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Cognitive-motor interference during postural control indicates at-risk cerebellar profiles in females with the *FMR1* premutation

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Glossary: *FMR1* gene = fragile X mental retardation 1 gene; FMRP = Fragile X Mental Retardation Protein; FXTAS = Fragile X Tremor Ataxia Syndrome; PM-carrier = Premutation carrier.

Abstract

Recent investigations report a higher risk of motor symptoms in females with the *FMR1* premutation (PM-carriers) than has hitherto been appreciated. Here we examined basic sensorimotor and postural control under different sensory and attentional dual-task demands. Physiological performance and postural sway measures from the Physiological Profile Assessment (Lord et al., 2003) were conducted in 28 female PM-carriers (mean age: 41.32 ± 8.03) and 31 female controls with normal *FMR1* alleles (mean age: 41.61 ± 8.3). Multiple regression analyses was conducted to examine the moderating role of CGG-repeat length on the relation between age and postural sway under dual-task interference. In female PM-carriers, our results showed significantly poorer proprioceptive awareness, slower reaction time, and greater postural displacement when performing a concurrent verbal fluency task. Significantly, these findings showed age- and genetically-modulated changes in dual-task postural displacement in the medio-lateral direction in female PM-carriers. These findings highlight the sensitivity of postural control paradigms in identifying early cerebellar postural changes that may act as surrogate markers of future decline in female PM-carriers.

Keywords: Fragile X Tremor Ataxia Syndrome (FXTAS); Fragile X Mental Retardation gene 1 (*FMR1*); Fragile X Mental Retardation protein (FMRP); Cerebellar motor networks; Cognitive-neuromotor interaction; Physiological Profile Assessment; Postural control

1. Introduction

Fragile X syndrome (FXS) is a neurodevelopmental disorder resulting from transcriptional silencing of the *FMR1* gene on the X chromosome. This silencing is associated with a large expansion of a CGG trinucleotide repeat in the 5' untranslated region and varying sizes of expansion can result in a continuum of fragile X-associated disorders. In FXS, there is a large expansion of the CGG repeat sequence (>200) and low production of the fragile X mental retardation protein (FMRP). Because FMRP is involved in normal brain development, through its impact on synaptic formation and function, reduced FMRP levels result in the characteristic intellectual impairment, autism and neurobehavioural profile associated with this condition [1, 2]. In recent years, much research has focused on individuals who have a medium-sized CGG-expansion on their *FMR1* gene (CGG> 55-200), known as premutation carriers (PM-carriers). Emphasising the need to investigate any neurobehavioural consequences in PM-carriers, the population incidence of PM-carriers is high with an estimated 1 in 209 females and 1 in 430 males with the PM in North American populations [3].

Emerging evidence now indicates that the carrier status is not “phenotypic free” as previously assumed, but rather has clinical and behavioural phenotypes associated with an increased risk for the late onset of a neurodegenerative disorder, fragile X-associated tremor ataxia syndrome (FXTAS). FXTAS occurs in approximately 45% of male PM-carriers and 8-16% of female PM-carriers over the age of 50 [4, 5]. FXTAS is associated with progressive dementia, intention tremor and ataxia alongside mood and global executive function deficits [4, 6, 7]. The protective effect of a normal allele on the second X chromosome in females can result in a milder clinical and pathological presentation than in male carriers. Female carriers may develop fragile X-associated primary ovarian insufficiency

(FXPOI) a term encompassing irregular periods, fertility problems, elevated follicle stimulating hormone (FSH) and early menopause. Approximately 20-28% of female PM carriers will have premature menopause (<40 years). There are also increasing reports of neurodegenerative disorders including Parkinsonism and Alzheimer's disease [8-10]. Recent findings indicate that impairments in executive working memory, inhibitory control and visuospatial processing begin as early as middle adulthood, and progressively deteriorate with increasing age and CGG repeat size in male PM-carriers [11-15]. However it remains unclear whether female PM-carriers show age-related neurocognitive impairments, resulting in neurodegenerative decline or a milder phenotype. Interestingly, recent investigations have identified abnormal psychomotor ability, age- and genetically-modulated visuospatial impairments, and greater deterioration with age in executive aspects of organisation and planning, in female PM-carriers [16-21].

In addition to neurocognitive impairments in female *FMR1* premutation carriers, there is emerging behavioural and imaging evidence of dysfunction along neuromotor circuitry in both male and female PM-carriers (see [21] for a review). Although structural changes associated with reduced grey matter volume in cerebellum, cortical and subcortical areas are a prominent feature in FXTAS, recent studies have revealed cerebellar abnormalities in anterior vermis and middle cerebellar peduncles in male PM-carriers who are asymptomatic for FXTAS [22, 23]. The anterior vermis, known to play a critical role in postural control [24, 25], may represent the earliest changes marking the imminent onset of ataxia, a core feature of FXTAS. Behavioural studies, using the coordination tremor balance test system (CATSYS), a quantitative assessment of tremor and postural sway, have shown that ataxia can be detected in 30% of male PM-carriers who were not aware of any balance problems [26]. However, a limitation of the CATSYS is the lack of sensitivity to subtle

changes in tremor (intention and postural) and postural sway in asymptomatic PM-carriers that may serve as surrogate markers of the imminent onset of neurodegenerative decline [19, 27]. Significantly, daughters of men with FXTAS self-report more balance and memory problems when compared to carriers without a family history of FXTAS [18], and on the CATSYS female PM-carriers show higher postural sway with eyes closed when compared to controls, albeit the differences do not remain significant after correction for multiple comparisons [19]. There is also evidence from both male and female PM-carriers to show age- and CGG-dependent impairments on tasks that are sensitive to processing within dorsal stream networks (known to subserve visuomotor processing), alongside preserved performance on tasks sensitive to processing in ventral stream networks (known to subserve object recognition) [14, 28, 29]. Because the parietal dorsal stream and cerebellar networks have been implicated in 'internal models' which are important for maintaining and monitoring conceptualisations of our 'body parts in space' [30], maturational problems within these networks may lead to abnormalities in the development of the postural control system [31]. Taken together, these findings raise the possibility of a subtle neuromotor profile in female PM-carriers, which may indicate the earliest changes to vulnerable neural circuits, prior to the onset of more severe clinical decline.

However, postural control requires maintenance by higher order attentional networks and involves complex multisensory integration based on vestibular, visual and somatosensory input [30, 32, 33]. The attentional demands on postural control are commonly examined using the dual-task paradigm, which presumes that performing a secondary cognitive task during the regulation of postural control will compete for limited attentional resources between the two tasks [30, 34]. Dual-task interference effects on postural control may depend on the nature and complexity of the cognitive or motor task,

and individual differences in cognitive and sensorimotor control. Previous reports have shown that elderly individuals with Alzheimer's disease show greater dual-task effects on postural control when compared to older people without cognitive impairment [35], which may also be related to an increased risk for falls [36]. Given the emerging profile of subtle attentional control difficulties across several domains in female PM-carriers, dual-task paradigms may offer a sensitive approach for detecting early neuromotor changes which may indicate the onset of more severe neurodegenerative decline.

In this study we explore for the first time postural control under different sensory and attentional demands through manipulation of visual, proprioceptive and cognitive input in young female PM-carriers. To assess physiological functions involved in postural stability, we employed a well-validated measure of physiological performance across different sensory and motor systems including vision, proprioception, muscle strength, reaction time and balance [37-39]. We examined postural sway (along both anterior-posterior and medio-lateral directions) during steady stance while manipulating proprioceptive and visual input in female PM-carriers when compared to age-matched controls with normal alleles. The impact of performing a secondary excluded-letter verbal fluency task [40, 41] on postural sway was also explored to examine the interrelationships between weaknesses in inhibitory control, processing speed and postural stability in female PM-carriers. Further, we examined whether dual-task interference effects on postural control show age- and CGG-repeat dependent changes in a subset of at-risk females with the *FMR1* premutation.

2. Methods

2.1. Subjects

Female PM-carriers were recruited through support groups and population-based fragile X carrier screening studies. Female control participants were also recruited through population-based fragile X carrier screening studies, and through local networks and via online advertisements. All participants were English speaking and had normal (or corrected) vision and hearing. Participants were excluded if there was a history of epilepsy or of a serious head injury, a previous diagnosis of a neuropathy or fibromyalgia, or any sign of intellectual disability as assessed using the Wechsler Abbreviated Scale of Intelligence (FSIQ<70). One PM-carrier tested positive as a full mutation after *FMR1* DNA testing and hence was excluded from the final analysis. The FXTAS Rating Scale [42] was used to screen all participants for features related to FXTAS—that is, tremor, ataxia or parkinsonism—or any other neuromotor disorder. The final analysis included 28 female PM-carriers aged between 22 and 53 years of age (mean age: 41.32), and 31 female controls with normal *FMR1* alleles aged between 22 and 55 years of age (mean age: 41.61). Both groups were matched on age, IQ and anthropometric characteristics. The descriptive statistics are shown in Table 1. All study participants provided signed informed consent and the study procedures were consistent with the Declaration of Helsinki and approved by the Southern Health Ethics Committee (project 10147B).

<INSERT TABLE 1 ABOUT HERE>

2.2. Molecular analyses

DNA was extracted from 2ml whole blood from all participants using the Promega Maxwell® 16 Instrument and associated Maxwell® 16 Blood DNA Purification Kit (Promega Cat No.: AS1010). PCR was performed using the Asuragen® AmplideX™ *FMR1* PCR Kit as this

assay has been shown to detect a full range of fragile X expanded alleles [43]. PCR products were assessed via capillary electrophoresis on an Applied Biosystems 3130 Genetic Analyzer with electropherogram analysis conducted using GeneMapper® software. All procedures were performed in accordance with manufacturer's instructions.

2.3. Short-form Physiological Profile Assessment

The short form PPA comprises validated measures of sensory and motor physiological function [39, 44]. First, *visual contrast sensitivity* was assessed with the Melbourne Edge Test [45], an A4 page of 20 circles split with two different shades of grey and at varying angles. The contrast between the two shades was increasingly difficult to ascertain, the highest level of difficulty (lowest contrast) correctly assessed was taken for further analysis. To assess simple *reaction time* participants responded to a red light located on a computer mouse, using their dominant hand to rapidly click the mouse button (5 practise and 10 test responses). We selected mean response time for further analysis. *Proprioception*, the sensory awareness of body parts in space, was assessed with a lower limb matching task [46]. Participants were seated on a tall chair with their eyes closed and made five successive attempts at raising and matching their big toes on either side of a large protractor (See Figure 1). The number of degrees between each big toe was recorded with the mean selected for further analysis. To examine *muscle force*, we gauged only knee flexion, where the participant sat on a tall chair and extended their dominant leg which had a Velcro strapped across the calf area and a weight attached. Of three trials, the greatest force was recorded (in kilograms).

<INSERT FIGURE 2 ABOUT HERE>

We further assessed *postural sway* with a sway meter, which is a mechanical device that records postural displacement at the level of the waist (see Figure 2). We recorded anterior-posterior (AP) and medio-lateral (ML) postural displacement in millimetres. The sway meter has been well validated with strong correlations with centre of pressure measures taken on a force plate [39, 47]. For the present study, we employed an extended version of the original 30-second sway meter task and manipulated visual, proprioceptive and attentional input. Specifically, participants completed four 60-second single-task trials - standing on the floor with eyes open and eyes closed, standing on 15cm thick high density foam to additionally reduce proprioceptive feedback with eyes open and eyes closed. For the postural sway dual-task, we examined the effect of a concurrent *excluded-letter-verbal-fluency* (ELVF) task which required generating as many words as possible within 60-seconds while inhibiting words containing a select vowel, proper nouns and repeats [48, 49]. The first fluency task was completed at baseline (while seated) (words with no “A”), and then while balancing on the floor (words with no “E”) and foam (words with no “I”) with performance measured as the number of correctly enumerated words. All postural sway tasks were in order of increasing difficulty as per previous recommendations [39].

2.4. Statistical analyses

Data were analysed using IBM SPSS Statistics 20.0. Normality was checked with the Shapiro-Wilk test and all outliers were adjusted to one value point above or below two standard deviations from the group mean [50]. Independent group t-tests were first used to compare group differences for the entire short-form PPA assessment and additional dual-

task conditions. A Bonferroni correction was made for each sensorimotor condition ($p < .013$), while p -values for postural control tasks were corrected on the number of levels within single-task ($p < .013$) and dual-task ($p < .025$) conditions. Following this we performed a series of multiple linear regression with interaction terms, with each dual-task postural control condition selected as the primary criterion measure, and the predictor variables as age, CGG repeat length and their interaction. In accordance with previously established guidelines [51], CGG repeat and age were centred prior to regression analyses and multiplied together to represent the interaction. The assumptions of multiple regression (i.e., independence of residuals, normality of residuals, linearity, and homoscedasticity) were met for these analyses.

3. Results

All participants completed physiological profile assessment (PPA) and dual-task conditions. Due to technical issues, which resulted in non-recording of results, performance data were only available on the excluded-letter-fluency-dual-task for 25 PM-carriers and 30 controls.

3.1. Sensorimotor function assessment

As evident in Table 2, between-group comparisons showed that when compared to controls, the PM-carrier cohort was comparable on measures of contrast sensitivity and leg strength, but showed slower motor reaction time ($p=.009$) and worse proprioceptive awareness ($p=.010$).

3.2. Performance of the verbal fluency task

PM-carriers performed significantly worse than controls on all three versions of the verbal fluency task (baseline: $t(57) = -4.066, p = .001$; verbal fluency-task standing on floor: $t(56) = -2.723, p = .009$; verbal fluency-task standing on foam: $t(53) = -2.435, p = .018$).

3.3. Balance performance

As shown in Table 3, PM-carriers showed significantly increased postural displacement when performing the concurrent verbal fluency task and standing on foam and on the floor when compared to controls. The higher postural sway in female PM-carriers was evident for both AP ($p = .012$) and ML ($p = .005$) directions relative to controls when standing on foam, and in the ML direction only when standing on the floor ($p = .024$). As shown in Figure 3, the control group showed improved postural performance in AP and ML directions for all dual-task conditions. Alternatively, PM-carriers showed improved postural performance in the AP direction for both dual-task conditions, however poorer performance was indicated by increased displacement in the ML direction during stance on the foam surface.

<INSERT TABLE 3 ABOUT HERE>

<INSERT FIGURE 3 ABOUT HERE>

3.4. Associations with CGG-repeat length and age

We employed regression analyses to examine the moderating role of CGG-repeat length on the relation between age and dual-task effects on postural control (see Table 4).

<INSERT TABLE 4 ABOUT HERE>

When standing on the floor, age showed a negative association with increased AP displacement during the verbal fluency dual-task condition ($p=.020$). There was also a significant positive association between CGG repeat length and ML displacement during the secondary task ($p=.029$).

For the standing on foam condition, there were no associations between age or CGG-repeat repeat and postural displacement in AP or ML directions. As shown in Table 5, there was a significant interaction between age and CGG repeat length for postural ML displacement (with eyes open) during the secondary verbal fluency task. This shows that CGG repeat length moderates the relationship between age and greater postural instability for ML displacement during dual-task performance in PM-carriers. For baseline verbal fluency, basic sensory and motor functions, there were no associations with age or interactions between age and CGG repeat length (please refer to supplementary Table e-1).

4. Discussion

This study is the first to examine postural control during concurrent manipulation of visual, proprioceptive and attentional demands in young female PM-carriers. Our findings indicate core impairments associated with dual-task interference effects on postural control in females with the *FMR1* premutation. The findings also emphasise the utility of dual-task paradigms in identifying age- and genetically-modulated changes in postural control which may be associated with at-risk profiles in female PM-carriers. These results extend previous studies which have employed self-report and standardised assessments of postural control in female PM-carriers [18, 19], to include a more sensitive experimental approach to dual-task effects on complex multisensory integration and postural stability. Although future

longitudinal studies will be critical in distinguishing between neurodegenerative and neurodevelopmental processes, these findings suggest that cerebellar networks underlying postural control may be especially vulnerable to the effects of the *FMR1* premutation.

Our results showing significantly increased dual-task effects on postural sway in female PM-carriers compared to controls are consistent with capacity interference caused by competition for limited attentional resources [30, 52, 53]. The contrasting pattern of findings in the control group, who showed improved postural displacement during performance of a concurrent verbal fluency task, is consistent with the contention that secondary cognitive tasks with low attentional demands may direct attention away from balance control, and shift postural performance to a more automatic state [52, 54]. In contrast, the poorer performance on verbal fluency and postural sway in female PM-carriers suggests that reduced attentional (inhibitory) control could result in performance that is closer to their stability boundaries. This interpretation is consistent with the pattern seen in patients with Parkinson's disease, where poor performance on secondary cognitive tasks typically compounds already compromised cognitive and postural control systems [55]. Consistent with this interpretation, we show that even though female PM-carriers show intact postural control during multi-sensory integration, the dual-task effects on increased medio-lateral sway may only become apparent under increasing demands on cognitive control. Given that early disturbances of executive control associated with postural instability may predict increased risk of falls, restricted mobility and progression to dementia [36, 56], the increased interference of an attention-demanding task on postural control in female PM-carriers may represent the earliest indicator of the onset of more severe age-related cognitive and motor decline.

In terms of neural basis for dual-task effects on postural control in female PM-carriers, existing imaging studies suggest that cortico-cerebellar pathways which functionally connect with higher level cognitive networks are disrupted in male PM-carriers with and without FXTAS [22, 23, 57, 58]. Previous imaging studies in asymptomatic *FMR1* premutation carriers show white matter alterations (demyelination and axonal damage) of the afferent projections of middle cerebellar peduncles (MCPs) and superior cerebellar peduncles [22, 57, 58]. These may be the earliest neuroanatomical markers of the onset of cognitive and motor symptoms associated with FXTAS. The MCPs include fronto-cerebellar tracts connecting to orbitofrontal and dorsolateral prefrontal cortices that are critical for cognitive control [59]. Moreover, a recent Transcranial Magnetic Stimulation (TMS) study has detected an absence of cerebellar inhibition over the primary motor cortex alongside deficient GABAergic mechanisms (reduced GABA-A mediated intracortical inhibition) in young female PM-carriers [60]. These alterations to cerebellar-cortico and cerebello-motor connectivity may well disrupt extensive brain networks subserving dual motor and cognitive performance in female PM-carriers. Indeed, network connectivity studies have shown that the cerebellum is critical for functional connectivity within cognitive- and motor-related regions necessary for efficient cognitive control during dual-task performance [61]. Together, these findings imply that cerebellar abnormalities may disrupt the integration and efficiency of widespread cognitive and motor networks critical for stable postural control in female PM-carriers.

The current findings on measures of sensory and motor physiological function suggest that female PM-carriers exhibit slowed psychomotor speed and reduced proprioceptive awareness but with no evidence for age-related decline. The presence of

slowed motor reaction time is inconsistent with previous studies which have reported enhanced basic psychomotor speed in female PM-carriers [62, 63]. One possible explanation for the discrepancy between these studies and our findings could be the higher mean age and range (mean age 41.32; range: 22-53) of the female-PM carriers in the current study. Consistent with this, simple reaction time to an auditory stimulus and finger tapping has been reported as being significantly slower in older (mean age 52.86) female PM-carriers without FXTAS [19]. Taken together with the findings of poorer proprioceptive awareness in female PM-carriers, the subtle proprioceptive and motor coordination deficits are consistent with disrupted cerebellar functioning. Proprioceptive information, which informs our sense of self-position and movement [64], is integrated within lower levels of the spinal cord and the cerebellum, where internal models for guiding movement are developed and regulated [65]. Significantly, although the motor coordination deficits are consistent with previous imaging studies showing cerebellar abnormalities in PM-carriers [23, 58], the poor integration of proprioceptive sensory input may well be associated with the previously reported peripheral and sensory neuropathies in female PM-carriers [66]. Given the lack of association with age and CGG repeat length or their interaction, we interpret the impairments in low level sensorimotor integration as reflecting likely neurodevelopmental changes that may present early in the developmental trajectory, possibly causing lifelong alterations to sensory and motor networks.

Our results showing age- and genetically-modulated cognitive and postural dual-task impairments suggest distinct molecular events operate in female PM-carriers with expanded repeats. This is consistent with previous studies which have indicated increased CGG-repeat vulnerability along neuromotor circuitry in female premutation knock-in (KI) mouse models [67, 68]. Furthermore, it highlights molecular evidence showing that increased levels of

FMR1 mRNA in high CGG repeat carriers is associated with moderately reduced FMRP levels presumably due to a deficit in translational efficiency [69, 70]. Although the *FMR1* mRNA elevations are the purported cause of FXTAS neuropathology [71], the RNA-binding protein FMRP, which is essential for synaptic maturation and neuronal plasticity, has been proposed to underlie a range of developmental cognitive problems associated with the *FMR1* premutation [16, 72-74]. In female PM-carriers, the diluting effect of X-inactivation skews the positive correlation between CGG repeat length and total *FMR1* mRNA levels [75]. In terms of risk of mild cognitive impairment, it has been shown that with increasing CGG repeat size (CGG >100) and reduced FMRP expression (<60% in hair roots), there is an increased decline in IQ scores in female *FMR1* premutation carriers [76], and hypermethylation of *FMR1* intron sites has been shown to predict verbal cognitive impairment [77]. Thus we speculate that the present findings of enhanced sensitivity to attentional demands on postural control in female PM-carriers may not only be associated with *FMR1* mRNA toxicity, but may also reflect greater neural susceptibility of cerebellar networks to the differential expression of the *FMR1* protein.

The use of a cross-sectional design is a limitation of the present investigation and longitudinal imaging studies examining structural and functional connectivity will be needed to identify cerebellar profiles that differentiate between neurodegenerative processes and subtle neurodevelopmental changes. Furthermore, it is not yet clear if these sensorimotor abnormalities and dual-task costs in postural control would show greater age-related decline in male PM-carriers with an increased risk for FXTAS. Future studies should manipulate attentional load across both cognitive and motor tasks to provide a more sensitive marker of age-related decline than otherwise detectable using gross neuropsychological measures in female PM-carriers. Finally, given that methylation patterns

and X-inactivation levels have been shown to skew relationships between CGG repeat length and both FMRP and *FMR1* mRNA levels [78, 79], further investigations of epigenetic markers and the molecular events downstream of the CGG repeat expansion on the *FMR1* allele are warranted.

In conclusion, the current findings highlight the sensitivity of dual-task postural control paradigms in examining the attentional demands on postural sway in young female PM-carriers. We contend that the cerebellar motor and cognitive networks are implicated in postural control difficulties, possibly as a result of *FMR1* mRNA toxicity and/or differential expression of the *FMR1* protein. The lack of an age-related decline in verbal fluency and low level sensory and motor physiological function may well reflect a stable developmental phenotype in female PM-carriers. Prospective longitudinal studies will be needed to evaluate the utility of dual-task postural paradigms in detecting subtle age-related decline associated with the onset of degenerative processes or more stable developmental changes. These investigations will be critical for the development of surrogate markers in both male and female PM-carriers for future use in therapeutic trials for FXS-associated disorders.

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7. Author contributions: Claudine Kraan, Darren Hocking and Kim Cornish (first, second and last author) conceptualized and designed the study, provided intellectual input into the interpretation of the data and co-wrote the first draft of the manuscript. Nellie Georgiou-Karistianis (3rd author) provided intellectual input into the interpretation of the data, as well as input into drafts of the manuscript. Sylvia Metcalfe and Alison Archibald (4th and 5th authors) contributed to study design, assisted with recruitment, facilitated genetic testing of participants, and contributed to the manuscript. Joanne Fielding (6th author) provided intellectual input into the drafting of the manuscript. Julian Troller (7th author) assisted the design of the study, critical review and revision of the manuscript and interpretation of results. John Bradshaw (8th author) provided intellectual input into the drafting of the manuscript and Jonathon Cohen (9th author) assisted with recruitment and contributed to drafts of the manuscript.

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Table 1

Means and standard deviations for sample characteristics for female FMR1 PM-carriers and control participants

	<i>FMR1</i> PM-carriers (N = 28)	Controls (N = 31)	p value
	M ± SD (range)	M ± SD (range)	
Age (years)	41.32 ± 8.03 (22-53)	41.61 ± 8.3 (22-55)	.892
FSIQ	109.41 ± 11.16 (88-128)	113.16 ± 7.86 (89-129)	.151
VIQ	105.07 ± 14.38 (73-126)	109.74 ± 10.41 (88-136)	.159
PIQ	110.71 ± 10.78 (87-133)	114.29 ± 9.31 (93-133)	.177
Height (cm)	162.04 ± 9.41 (129-174.5)	163.15 ± 19.73 (63.2-181)	.786
Weight (kg)	75.14 ± 24.23 (48-169)	75.89 ± 20.50 (52-152)	.897
CGG-repeat length	84.79 ± 14.67 (61-122)	31.30 ± 3.14 (28-42)	<.001**

Abbreviations: FSIQ = Full Scale Intelligence Quotient; PIQ = Performance Intelligence Quotient; SD = Standard Deviation; VIQ = Verbal Intelligence Quotient.

** $p < .01$

Table 2

Means and standard deviations for sensorimotor assessments for PM-carriers and control participants

	<i>FMR1</i> PM-carrier M ± SD	Control M ± SD	<i>p</i> -value
Contrast sensitivity	22.43 ± 1.26	22.06 ± 1.32	.283
Reaction time (milliseconds)	222.37 ± 34.26	200.77 ± 26.65	.009*
Proprioception (degrees)	.90 ± .52	.56 ± .47	.010*
Leg strength (kg)	20.68 ± 5.72	20.65 ± 5.60	.982

**p* < .013

Table 3

Means and standard deviations for postural control displacement in millimetres (mm) with sensory and cognitive interference manipulated for FMR1 PM-carriers and controls.

	<i>FMR1</i> PM-carrier	Control	<i>p</i> -value
Postural sway in mm (standing on floor)	M ± SD	M ± SD	
Single-task conditions			
Eyes open on floor AP	20.46 ± 7.32	19.44 ± 5.52	.542
Eyes open on floor ML	19.38 ± 13.15	19.07 ± 11.91	.925
Eyes closed on floor AP	22.00 ± 7.76	21.90 ± 6.96	.960
Eyes closed on floor ML	14.41 ± 10.11	14.05 ± 9.41	.887
Eyes open on foam AP	33.43 ± 14.47	29.61 ± 9.00	.224
Eyes open on foam ML	27.70 ± 16.53	25.00 ± 11.93	.472
Eyes closed on foam AP	44.71 ± 9.35	42.23 ± 13.74	.425
Eyes closed on foam ML	42.89 ± 24.40	37.81 ± 15.51	.339
Dual-task conditions			
Eyes open dual-task floor AP	19.46 ± 7.16	19.13 ± 6.34	.849
Eyes open dual-task floor ML	19.46 ± 11.77	13.48 ± 7.04	.024*
Eyes open dual-task foam AP	33.27 ± 11.14	26.86 ± 7.05	.012*
Eyes open dual-task foam ML	33.32 ± 18.97	21.37 ± 11.63	.005**

Abbreviations: AP = Anterior-posterior direction; *FMR1* = Fragile X Mental Retardation 1 gene; ML = Medio-lateral direction

* $p < .025$, ** $p < .01$,

Table 4

Standardised β and t values for the continuous moderator variable of CGG repeat length in the moderator regression analyses for the relation between age and postural displacement under cognitive interference for PM-carriers

	On floor				On foam			
	Eyes open AP		Eyes open ML		Eyes open AP		Eyes open ML	
	S β	t	S β	t	S β	t	S β	t
Constant		2.650		.331		1.358		.590
CGG length	.328	1.744	.433	2.330*	.129	.617	.349	1.924
Age	-.470	-2.498*	-.256	-1.377	.066	.315	-.209	-1.150
ageXCGG	-.010	-.057	.222	1.251	.161	.806	.376	2.173*
<i>R</i> ²		.234		.254		.053		.289*
<i>Adjusted R</i> ²		.138		.161		-.065		.201*

Abbreviations: AP = Anterior-posterior direction; ML = Medio-lateral direction; S β = Standardised Beta; t = test statistic.

* $p < .05$

Figure 1. The lower limb matching task used to index proprioception [41]

Figure 2. The sway meter task from the short form PPA consisted of a waist high 40cm-long-rod attached to a vertically mounted pen. This pen was placed on graph paper and postural displacement in both anterior posterior and medio-lateral directions was taken for further analyses (as indexed by movement of the pen). We examined postural displacement during stance on the floor (A) and stance on a high density foam surface (B). Image taken with permission from Lord et al., [41].

A.

B.

Figure 3. Postural control displacement in AP direction at baseline and under dual-task performance while standing on the floor with eyes open (A) and on foam with eyes open (B) and postural control displacement in ML direction at baseline and under dual-task performance while standing on the floor with eyes open (C) and on foam with eyes open (D) for PM-carriers and control participants. These graphs show that for AP spatial displacement, both controls and PM-carriers showed maintenance or even improved performance in the dual-task condition. In the ML direction controls showed maintenance or improvement of performance when the dual-task was added, and by contrast, PM-carriers showed an increase in postural displacement reflective of a worsening in performance.

Highlights

Female premutation carriers have a defective CGG trinucleotide expansion on the *FMR1* gene

This CGG expansion is associated with a high risk for ataxia motor symptoms

We showed enhanced dual-task postural displacement in asymptomatic female carriers

Dual-task postural displacement also associated with age- and CGG-length

Postural control paradigms may identify early cerebellar changes in female carriers

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