Decreased Theta Power Reflects Disruption in Postural Control Networks of Fragile X Premutation Carriers *

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Abstract— FRM1 premutation carriers exhibit various subtle deficits in balance and stability, prior to the development of the movement disorder Fragile X Associated Tremor/Ataxia Syndrome (FXTAS). Force plate posturography has increasingly been combined with the temporal sensitive imaging methods such as EEG to offer insight into the neural mechanisms which govern postural control. This study investigated cortical theta power during continuous balance and its relationship to balance performance in Fragile X premutation carriers. Eight premutation carriers and 6 controls stood on a force platform under altered sensory and cognitive conditions while postural sway and high-density EEG data were simultaneously recorded. Carriers exhibited greater sway area when sensory input was reduced (p=0.01) and cognitive load was increased (p=0.01), as well as significantly reduced frontal theta power compared to the Control Group. The relationship between theta power and postural control seen in the control group may indicate an increase in error detection caused by reduced visual input and greater discrepancies between expected and actual balance state. While the lower theta power in frontal regions of carriers may indicate a disruption in neural networks underpinning postural control. Such results provide new insight into the neural correlates of balance control in Fragile X premutation carriers.

I. Introduction

Fragile X Associated Tremor/Ataxia Syndrome (FXTAS) is a neurodegenerative movement disorder caused by a CGG trinucleotide repeat expansion and characterized by intention tremor, ataxic gait, balance impairments, and progressive cognitive decline [1-3]. FXTAS affects between 16-40% of FMR1 premutation carriers over the age of 50 [3], yet it is not understood why this proportion of carriers develop FXTAS or how to predict those who might be at risk. However, carriers have also reported impaired motor control before the typical age of onset such as impaired static and dynamic balance as well as longer response times to balance perturbations compared to controls [4, 5]. Therefore, measures of postural control may provide sensitive indicators to motor system dysfunction for tracking disease onset in younger PM carriers. Despite the growing interest in motor deficits in younger carriers, there has been very little research into the neural mechanisms that underpin these motor systems. The FMR1 premutation results in widespread progressive neuropathology, leading to the clinical phenotype associated with FXTAS. Structural MRI studies reveal generalized brain atrophy, particularly the cerebellum, as well as white matter degeneration throughout the cortex in carriers with FXTAS [6, 7]. Such regions are involved in the cortico-cerebellar feedback loop which is vital for adaptive postural responses [8]. However neural activity has not yet been explored in the context of postural control in younger premutation carriers.

Postural control is a dynamic process involving cognitive and sensory input as well as motor functioning, therefore the focus of recent studies has turned towards the role of cortical regions in the initiation and regulation of postural control [8-11]. For example, the Posterior Parietal Cortex (PPC) which processes sensory information, sensory-motor transformation, and is highly integrated with motor and premotor areas [12, 13]. Similarly, the Anterior Cingulate Cortex (ACC) has been implicated in balance control due to its involvement in action monitoring and error detection [14]. EEG studies have demonstrated increased cortical theta power in the ACC during single-leg stance [15, 16] and balance beam walking [14], while other studies have also demonstrated fronto-central activity at the limit of stability, when the expected balance state is incongruent with actual balance [11, 17], therefore emphasizing the role of the cortex is maintaining balance and stability.

This study aimed to employ force plate posturography measures and high-density EEG recordings to characterize the postural phenotype of younger FMR1 premutation carriers and the neural mechanisms underpinning continuous balance and signaling of instability in carriers. Based on previous reports, we hypothesized that premutation carriers would exhibit decreased stability compared to controls during challenging balance tasks and that this change in stability would be reflected by a change in activity of the neural substrates governing postural control.

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TABLE I. DEMOGRAPHIC DETAILS

	PM Carriers n=8	*Control Group n=6*	*p-value*
Age (years)	41.8 ± 3.7	35.6 ± 6.1	0.03*
Height (cm)	165.17 ± 6.45	171.03± 69.57	0.31
Weight (kg)	79.8 ± 18.25	69.75 ± 13.8	0.27
CGG repeats	83.33 ± 10.98	-	-
SART (correct)	21.7 ± 1.98	22.0 ±1.7	0.81
N-Back (%correct)	91.16 ± 8.8	94.6 ±8.45	0.47

PM=Premutation Carriers *=denotes significance to $p<0.05$

II. METHOD

A. Participants

Participants consisted of 8 Premutation Carriers (1 male, age: 41.8 ± 6.8 years) and 6 Controls (2 males, age 35.6 ± 6.1 years). See Table 1 for summary demographics. No participant reported a history of neurological or musculoskeletal disorders. Informed consent was obtained from all participants and the protocol was approved by Tallaght University Hospital and St. James' Hospital Joint Research Ethics Committee.

B. Postural Control Task

Participants stood comfortably with arms by their sides, near the center of the force platform (Biosignals Plux, Portugal). An eye-level visual reference was presented on a screen 1.5 m from the subject. Without moving their feet, participants were asked to stand quietly during four conditions. Three 60 s trials were carried out with a single task- standing with eyes open (EO) or Eyes Closed (EC) and two dual-task conditions- A working memory-based N-back task and a Sustained Attention to Response Task (SART) [18]. Subjects used a push button to provide responses to tasks. Cognitive tasks were presented at random with EO and EC conditions interspersed between cognitive tasks.

C. Centre of Pressure Data Analysis

Force plate data were sampled at a frequency of 1000Hz, then downsampled to 50 Hz [19]. A 4th order lowpass Butterworth filter, with a cutoff frequency of 10 Hz was used to remove noise [20]. Classic Centre of Pressure (COP) sway parameters were calculated, including sway area via a 95% confidence ellipse, path length and velocity in the anterior-posterior (AP) and mediolateral (ML) directions.

D. EEG Data Collection

EEG data were recorded with a Biosemi ActiveTwo 128-Channel 24bit system, sampled at 2048Hz and electrode impedance was kept below 5kΩ. All processing was performed using the open-source Matlab based EEGLAB toolbox [12] (MathWorks, Inc., Natick, MA).

The EEG data were resampled offline at 256 Hz and filtered with a bandpass filter with a bandwidth of 1-45 Hz. Artifacts were identified through ICA and by visual inspection and removed using ADJUST function in EEGlab, bad channel data were interpolated and referenced to the common average. Based on recommendations by Slobounov et al. [11] Four regions of interest (ROIs) were defined and adapted to the 128 channel Biosemi electrode system. ROIs included fronto-medial (AFz Fz FCz F2 F1), frontal (AF1 Fz AF2 F8 F7 F3 F4), Central (C3 C4 C1 C2 Cz CP1 CP2) and parietal (Pz P1 P2 P3 P4 PO3 PO4 P8 P7).

E. EEG Data Analysis

The EEG signal for each balance task was divided into 2s epochs with a 50% overlap. Theta frequency (4-7Hz) was extracted and mean spectral power (μV^2) was calculated by averaging power values of electrodes in each ROI. The natural logarithm (ln) was applied to absolute ROI values to approximate a normal distribution.

F. Statistics

To account for the limited sample size and non-normal distribution of some parameters, non-parametric statistics were used for analysis. Mann-Whitney U tests were used to the compare performance of postural control between groups. Friedman's tests were used to assess changes within each group across the four postural control tasks, as well as changes across ROIs. Where significant differences were found, Wilcoxon signed-rank tests were carried out and Bonferroni corrections were applied. Correlations between postural control and neural activity were carried out using Spearman's Rho. Due to the well-established impact of FMR1 CGG repeat length and age on symptom severity in Premutation Carriers, a one-tailed Spearman's Rho correlation was carried out to assess the relationship between repeat length or age and postural control.

III. RESULTS

A. Postural Control Data

Between-group analysis did not reveal significant differences in postural sway performance as determined by classical sway parameters ($p<0.05$). When sway parameters were compared with the performance during baseline EO conditions, Premutation Carriers did display increased path length during the EC condition, as well as during both SART and N-back tasks ($p=0.012$ for all). Similarly, carriers exhibited greater sway area during both dual-tasks ($p=0.012$ for N-back, $p=0.017$ for SART) compared to EO stability measures. There was no change in velocity across conditions. Sway parameters of the Control Group remain consistent across all four conditions ($p>0.05$).

B. EEG results

Between-group analysis of EEG data revealed a significant difference in theta power between groups during the eyes open condition, whereby the premutation carrier group exhibited significantly lower levels of theta power in frontomedial regions compared to the Control Group ($U=3.0$, $p=0.007$). Frontal and parietal regions were also higher than that of the Premutation carrier group but did not reach the level of significance when adjusting for multiple tests ($p=0.02$ for both).

During the N-back task, theta power in the fronto-medial region of the Control Group was higher than that of the Premutation Carrier group but this difference did not survive

correction for multiple comparisons (U=6.0, p=0.02). Theta power for both groups was comparable across regions during the EC condition and the SART task (p>0.05). See Fig. 1.

Friedman's test did not reveal a change in Premutation Carrier's theta power across fronto-medial regions ($\chi^2(3)$ = =4.05, p=0.256) or central regions for $\chi^2(3)$ =3.0, p=0.392. While there was evidence of a change in parietal activity across tasks, $\chi^2(3)$ =8.25, p=0.04, Wilcoxon post-hoc follow up tests revealed higher theta power during EO condition than the EC condition and both dual tasks, these differences did not withstand adjusting for multiple tests. Theta power in the Control group also remained consistent across tasks in each ROI.

C. Correlations

Spearman's Rho correlation analysis was carried out to assess relationships between sway parameters and neural activity in both groups. There was a strong inverse correlation between sway parameters, specifically mediolateral sway velocity and theta power in both frontal and central regions (p=0.0001, r_s= -0.86, for both; see Fig. 2). as control subjects stood with their eyes closed, whereby velocity increased as theta power decreased. Mediolateral velocity also appeared to be correlated frontal theta during the EO condition (p=0.04 r_s=-0.829), central theta during the N-back task (p=0.03, r_s=-0.9), and parietal theta during the SART task (p=0.03 r_s=-0.92) for the Control Group, however, these correlations did not survive correction for multiple comparisons. There was no such relationship between postural parameters and neural activity evident within the Premutation Carrier Group.

The number of CGG repeat lengths were significantly inversely correlated with sway speed, particularly in the anterior-posterior direction where greater CGG repeat length was associated with slower sway speed (p=0.004, r_s=-0.883). There was no correlation between age and postural performance or neural activity for either group (p>0.05).

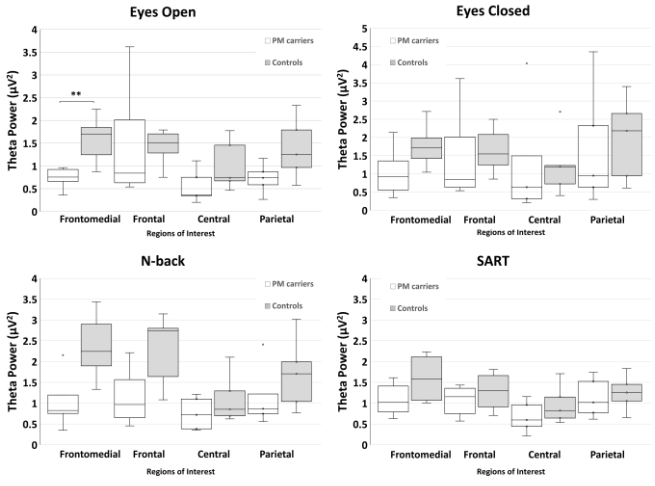

Figure 1. Theta power for each group during four conditions. Shaded boxes indicate control subjects Eyes Open (top left), Eyes Closed (top right), N-back (bottom left) and SART (bottom right). ** denotes significance to the level of p<0.01

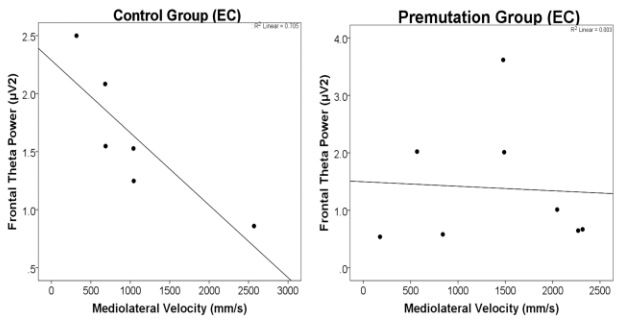

Figure 2. Correlation between Velocity in mediolateral direction and theta power for the control group (left) and Premutation Group (right).

IV. Discussion

This study aimed to employ force plate posturography combined with high-density EEG analyses to explore changes in postural stability of younger Premutation Carriers and to investigate the neural mechanisms than may underline these changes. The results of this study suggest there are substantial changes in Premutation Carriers' ability to maintain consistent balance when postural control is challenged with increased cognitive and sensory demands. These changes in postural performance were accompanied by different patterns of neural activity when compared to the Control Group.

There is a growing body of evidence describing subtle changes in motor behavior of younger Premutation Carriers before the typical age of onset of FXTAS. Several studies have described balance as a primary domain affected in younger carriers both when sensory input is challenged [4, 5] and as cognitive load is increased [21-23]. In line with such studies, the classical sway parameters measured during this study suggest carriers exhibit reduced stability both when eyes were closed, and while engaged in cognitively strenuous tasks. This may suggest capacity interference during dual-tasks, which may result from an inability to efficiently divide attentional resources to cater for additional demands [24].

Contrary to this, the postural performance of the Control Group remained consistent during the more demanding tasks. However, theta power, particularly in frontal regions, was greater for the Control Group across all conditions but most significantly so at baseline stability and again during the N-back task. This greater frontal theta power may reflect activity in the anterior cingulate cortex, a region known for involvement in action monitoring and error detection [14]. Higher levels of theta power are believed to reflect the generation of error signals to maintain balance when stability is challenged [9].

The associations found between postural sway parameters, such as the speed of sway, and neural activity in the Control Group lends further support to this line of reasoning. Despite exhibiting decreased stability during conditions where balance was challenged, Premutation Carriers did not display a change in theta power, nor was there evidence of a link between neural activity and postural performance, as was observed in the Control Group. The link between neural

activity and postural sway in the Control Group was particularly evident while visual input was limited, therefore forcing subjects to rely on alternative sensory input to remain steady. Increased activity distributed over frontal and parietal region is believed to reflect the transfer of sensory information from parietal regions to anterior cingulate areas for processing and error detection [9, 11, 14].

The cumulative pattern of the above results from these experiments and the dissociation between theta power and postural control observed in the premutation carrier group may indicate a disruption in the neural pathways that underpin error detection in postural stability. Future studies may benefit from employing more subtle measures of postural control such as entropy-based measures to assess changes in stability[21]. The sample size of this study is also limited, therefore, large scale, longitudinal, and age-matched studies would be needed to determine if this results from a stable developmental change resulting from the FMR1 premutation, or the beginning of neurodegenerative processes associated with FXTAS, however, the findings of the current research sheds new light on the neural correlates of postural control in younger fragile X Premutation Carriers and emphasizes the utility of temporally sensitive neuroimaging methods in characterizing these changes.

V. Conclusion

To conclude, this study expands on previous research into cortical structures underlying continuous postural control and sheds light on potential disruptions in regions involved in processing information related to stability maintenance, in a cohort experiencing balance issues. Such findings may subsequently lend to the establishment of biomarkers to allow for earlier diagnosis of movement disorders such as FXTAS and the development of rehabilitative measures to improve stability and quality of life.

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