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ORIGINAL RESEARCH

# Reduced caudate volume and cognitive slowing in men at risk of fragile X-associated tremor ataxia syndrome

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## Abstract

Fragile X-associated tremor ataxia syndrome is an inherited neurodegenerative disorder caused by premutation expansions (55–200 CGG repeats) of the *FMR1* gene. There is accumulating evidence to suggest that early cognitive and brain imaging signs may be observed in some premutation carriers without motor signs of FXTAS, but few studies have examined the relationships between subcortical brain volumes and cognitive performance in this group. This study examined the relationships between caudate volume and select cognitive measures (executive function and information processing speed) in men at risk of developing FXTAS and controls with normal *FMR1* alleles (<45 CGG repeats). The results showed that men with premutation alleles performed worse on measures of executive function and information processing speed, and had significantly reduced caudate volume, compared to controls. Smaller caudate volume in the premutation group was associated with slower processing speed. These findings provide preliminary evidence that early reductions in caudate volume may be associated with cognitive slowing in men with the premutation who do not present with cardinal motor signs of FXTAS. If confirmed in future studies with larger PM cohorts, these findings will have important implications for the identification of sensitive measures with potential utility for tracking cognitive decline.

**Keywords** *FMR1* premutation · Fragile X-associated tremor ataxia syndrome · Executive function · Information processing speed · Caudate

## Introduction

Fragile X-associated tremor ataxia syndrome (FXTAS) is an inherited adult onset neurodegenerative disorder caused by premutation (PM) CGG expansion (55–200 repeats) in the Fragile X Mental Retardation 1 (*FMR1*) gene (Hagerman et al. 2001). The syndrome affects approximately 45% of PM males aged over 50 years and 8–16% of PM females aged over 40 years (Rodriguez-Revenga et al. 2009), and is characterised by intention tremor, gait ataxia, parkinsonism, psychiatric disorder and cognitive decline. Primary cognitive deficits are observed in domains of executive function and information processing speed, consistent with disruption within fronto-subcortical circuits subserving cognitive and motor function (Birch et al. 2014). A number of molecular mechanisms have been suggested to contribute to the FXTAS phenotype associated with PM alleles, including elevated *FMR1* mRNA levels (Hagerman et al. 2001). Currently, the earliest indicators of risk for FXTAS and markers of progression are

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unknown, yet this knowledge is crucial for the development of preventive therapies and the design of future intervention trials.

Neuroimaging findings in patients with FXTAS have shown volume loss and white matter pathology within multiple cortical and subcortical brain regions, including the basal ganglia (Wang et al. 2013; Birch et al. 2017). Forming part of the striatum, the caudate is the major source of input to the basal ganglia receiving projections from multiple cortical regions implicated in higher order cognitive processes (Alexander et al. 1986). Deficits in executive function and information processing speed, primary cognitive features associated with FXTAS (Birch et al. 2014), are often observed in clinical populations with predominant caudate involvement (e.g. Huntington's disease; Ho et al. 2003, Domínguez et al. 2013). These features may be sensitive markers of striatal dysfunction even during pre-manifest stages of disease (Harrington et al. 2014); however, little research has investigated the sensitivity of such markers to disease progression. A multi-modal neuroimaging study of subcortical brain structures in PM males (Wang et al. 2013) found that significantly reduced white matter integrity (as measured by hypointensity on diffusion weighted imaging) of the caudate bilaterally was the most robust finding when comparing signal intensity in the thalamus and basal ganglia of PM males with FXTAS and controls. Further, smaller left caudate volume was associated with more advanced FXTAS stage. This suggests that degeneration of the caudate may underlie clinical manifestations of FXTAS, providing an opportunity for evaluation as a sensitive marker of vulnerability for decline. However, little is known about the relationship between caudate volume and cognitive changes prior to the onset of FXTAS.

Cognitive domains of executive function and information processing speed are the most prominent and well established cognitive markers of cognitive dysfunction in PM males both with (Grigsby et al. 2008) and without FXTAS (Cornish et al. 2008, 2011). Hence, these domains were selected for further investigation in the current study. The aim of this study is to examine whether caudate volume is associated with select higher order cognitive functions (executive function and information processing speed) in a cohort of PM males who do not meet diagnostic criteria for FXTAS, and in a comparison cohort of men with normal size *FMR1* alleles (<45 CGG repeats). It is hypothesised that: 1) PM males will have significantly reduced caudate volumes compared to controls; 2) Reduced caudate volume in PM males will be associated with poorer performance on cognitive domains of executive function and information processing speed; 3) Longer CGG repeat length and elevated *FMR1* mRNA levels in the PM group will be associated with smaller caudate volume and poorer cognitive performance.

## Materials and methods

### Participants

Fifteen PM males without FXTAS (aged 26–69 years) and 24 age- and education-matched controls with normal *FMR1* alleles (aged 26–77 years) were recruited as part of a study exploring cognitive and neuromotor profiles associated with the PM. Participants included in this report were recruited through genetic counselling services following cascade testing following diagnosis of a fragile X-associated disorder in another family member (i.e. none were a proband). For a full description of recruitment methods for this study see Birch et al. (2015). Neuropsychological data was incomplete for one PM male, *FMR1* mRNA level was missing for another PM male, and brain magnetic resonance imaging (MRI) was contraindicated for an additional two PM males in this report. All other participants met standard clinical criteria for MRI (i.e. they were free from incompatible implants or foreign metals in the body, etc).

### Neuropsychological assessment

Full scale intelligence quotient (IQ) was obtained using the four subtest version of Wechsler Abbreviated Scale of Intelligence (Wechsler 1999). Assessment of executive functions included measures of dynamic behavioral control and regulation (Behavioral Dyscontrol Scale 2) (Grigsby and Kaye 1996), phonemic fluency (Controlled Oral Word Association Test) (Spreen and Benton 1977), and response inhibition (interference trial of the Stroop Color and Word Test) (Golden and Freshwater 2002). Information processing speed was assessed using the Digit Symbol subtest of the Wechsler Adult Intelligence Scale III (Wechsler 1997), and the word reading and colour naming trials of the Stroop Color and Word Test (Golden and Freshwater 2002). Composite scores were used to reduce the number of variables to be used in the analyses and to reduce the risk of Type 1 error. Composite scores for cognitive domains of executive function and information processing speed were calculated as the first principal component of raw scores for each family of tests (higher score scores denote better performance). Factor loading scores for individual tests within each composite score were all high (≥.65) indicating that it was appropriate to reduce the data in this way.

### Brain MRI scans

A full description of the MRI protocol used for this study is provided in Birch et al. (2017). Briefly, brain MRI scans were conducted using a Phillips 3 T Achieva Quasar Dual Scanner (Phillips Medical Systems, Best, The Netherlands) located at Neuroscience Research Australia, Sydney. Three-dimensional T1-weighted scans were acquired using the following parameters: TR = 6.39 ms, TE = 2.9 ms, flip angle = 8°, matrix size =

256 × 256, FOV = 256 × 256 × 190, and slice thickness = 1 mm with no inter-slice gap, yielding 1 × 1 × 1 mm3 isotropic voxels. Volumes for left and right caudate volume were obtained by processing T1-weighted scans using the Functional MRI of the Brain Software Library v5.01 (Jenkinson et al. 2012). Estimated intracranial volume was generated using an atlas scaling and covariance approach as previously published (Buckner et al. 2004). Quality checking of segmentations followed ENIGMA protocols (http://enigma.ini.usc.edu) and included screening for outliers (outside 1.96 SD) and visual inspection of scans by a neuropsychiatrist (JNT). One outlier for caudate volume was identified (one PM male: left caudate z score = 2.22; right caudate z score = 2.01- positive score denotes greater volume). This scan was visually checked and confirmed to be a true value. Therefore, all caudate volumes met criteria for quality checking and were included in the analyses.

### Molecular analyses

Molecular analyses for this cohort have been previously described (Birch et al. 2015). In brief, CGG sizing and confirmation of PM status were performed using the Asuragen® AmplideX™ *FMR1* PCR Kit and methylation sensitive Southern blot analysis, respectively. EpiTYPER system methylation analysis was used to rule out presence of methylated *FMR1* alleles. *FMR1* mRNA analysis in peripheral blood mononuclear cells was performed using semi-quantitative reverse transcription real-time PCR standard curve method, with *FMR1* output normalized to mean expression of two internal control genes (SDHA and EIF4a2) as previously described (Shelton et al. 2017).

### Statistical analysis

Data were analysed using IBM SPSS Statistics Version 22. Normality was assessed using the Shapiro-Wilk test. Group differences in demographic and general sample characteristics between PM males and controls were tested using independent *t*-tests or Mann Whitney U where data were not normally distributed. Group differences in composite scores for executive function and information processing speed were assessed using MANCOVA, controlling for age. Total, left and right caudate volumes of PM males and controls were compared using MANCOVA, controlling for age and intracranial volume. Partial Pearson correlations were used to examine relationships between cognitive scores and total caudate volume, controlling for age and intracranial volume. Relationships between *FMR1* molecular measures (CGG repeat length and *FMR1* mRNA level) and both cognitive performance and total caudate volume were assessed using Partial Pearson correlations controlling for age, and age and intracranial volume, respectively.

## Results

### Cohort characteristics

The PM and control groups were well matched with no significant differences in age ($t_{(37)} = -1.589$, $p = .120$), education ($t_{(37)} = .086$, $p = .932$), or full scale IQ ($t_{(37)} = -.328$, $p = .745$) (Table 1). *FMR1* mRNA levels were significantly higher in the PM group compared to controls (Mann-Whitney $U = 57.000$, $p < .001$).

### Between-group differences in composite cognitive scores

Raw scores on individual cognitive tests are presented in Table 2. PM males attained significantly lower composite scores for executive function ($F_{(1,35)} = 6.007$, $p = .019$) and processing speed ($F_{(1,35)} = 4.813$, $p = .035$) compared to controls (Fig. 1).

### Between-group differences in caudate volume

PM males had significantly smaller total caudate volume compared to controls ($F_{(1,33)} = 6.681$, $p = .014$); both left ($F_{(1,33)} = 8.274$, $p = .007$) and right ($F(1,33) = 4.567$, $p = .04$) caudate volumes were significantly reduced (Table 3).

### Relationships between caudate volume and cognitive performance

In PM males, there was a strong positive correlation between total caudate volume and information processing speed ($r = .699$, $p = .025$). Although this relationship was not significant in controls ($r = .332$, $p = .131$) (Fig. 2), the correlation slopes in the PM and control groups were not significantly different (z = 1.306, $p = .192$). There were no significant correlations between executive function and total caudate volume in PM males ($r = -.039$, $p = .916$) or controls ($r = .383$, $p = .079$).

### Relationships between FMR1 molecular measures (CGG repeat length and FMR1 mRNA level), cognitive performance, and caudate volume in PM males

There were no significant relationships between any of the *FMR1* molecular measures and executive function (CGG: $r = -.108$, $p = .726$; *FMR1* mRNA: $r = .157$, $p = .627$), information processing speed (CGG: $r = -.231$, $p = .448$; *FMR1* mRNA: $r = -.110$, $p = .735$) or total caudate volume (CGG: $r = -.499$, $p = .118$; *FMR1* mRNA: $r = -.303$, $p = .395$) in PM males.

**Table 1** Sample characteristics

| | | PM ($n = 15$) | HC ($n = 24$) |
|---|---|---|---|
| Age (years) | Mean (SD) | 47.80 (14.06) | 55.33 (14.60) |
| | Range | 26–69 | 26–77 |
| Education (years) | Mean (SD) | 13.60 (3.64) | 13.50 (3.44) |
| | Range | 9–21 | 9–20 |
| Full scale IQ | Mean (SD) | 112.33 (8.54) | 113.46 (11.43) |
| | Range | 92–127 | 86–133 |
| CGG repeats | Mean (SD) | 87.33 (19.06) | 29.88 (4.09) |
| | Range | 72–134 | 20–44 |
| *FMR1* mRNA | Mean (SD) | 2.23 (1.29)*** | 1.18 (.28) |
| | Range | .92–5.76 | .71–1.69 |

*PM*, premutation; *HC*, control. *FMR1* mRNA was missing for one PM male

***$p < .001$

## Discussion

This study is the first to examine the relationships between caudate volume and cognitive function in PM males at risk of developing FXTAS. The results showed that PM males without FXTAS performed worse on measures of executive function and information processing speed, and had significantly reduced caudate volume relative to controls. Importantly, smaller caudate volume in PM males were associated with slower processing speed, providing preliminary evidence that early reductions in caudate volume may be associated with cognitive slowing in PM males. These findings add to a growing body of literature to suggest that early cognitive and radiological signs may be observed in PM males who do not present with cardinal motor signs and symptoms of FXTAS.

**Table 2** Raw scores on individual cognitive tests

| | | PM | HC |
|---|---|---|---|
| BDS | Mean (SD) | 22.87 (2.42) | 23.38 (3.35) |
| | Range | 20–27 | 13–27 |
| COWAT | Mean (SD) | 33.47 (12.14) | 39.92 (14.18) |
| | Range | 17–57 | 17–79 |
| Stroop CW | Mean (SD) | 35.64 (9.04) | 40.08 (12.93) |
| | Range | 17–47 | 20–68 |
| Digit Symbol | Mean (SD) | 65.87 (16.67) | 68.50 (17.03) |
| | Range | 39–100 | 30–97 |
| Stroop C | Mean (SD) | 66.93 (8.19) | 68.75 (12.03) |
| | Range | 57–83 | 44–91 |
| Stroop W | Mean (SD) | 90.00 (11.25) | 99.08 (18.14) |
| | Range | 65–107 | 73–150 |

*PM*, premutation; *HC*, control; *BDS*, Behavioral Dyscontrol Scale; *COWAT*, Controlled Oral Word Associated Test; *Stroop CW*, Stroop Colour-Word Interference score; *Stroop C*, Stroop colour naming score; *Stroop W*, Stroop word reading score

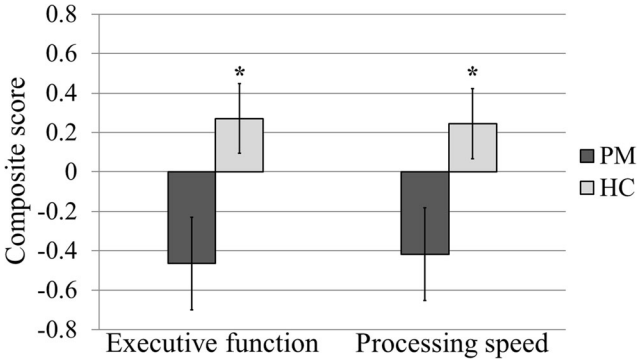


**Fig. 1** Estimated marginal means for executive function and processing speed composite scores (adjusted for age). Composite scores were missing for one PM male. PM = premutation; HC = control, *$p < .05$

In the current study, PM males without FXTAS demonstrated significantly poorer performance on cognitive measures of executive function and processing speed compared to controls. Features of executive dysfunction and cognitive slowing, which are frequently observed in other neurodegenerative disorders such as Huntington's disease (Ho et al. 2003), are consistent with dysfunction within fronto-subcortical circuits underlying cognitive and motor function (Alexander et al. 1986). The finding of poorer executive function performance among PM males is consistent with previous findings suggesting that a subset of PM males without FXTAS present with evidence of executive dysfunction (Cornish et al. 2008, 2011). However, to our knowledge, this study is the first to report a significant difference in processing speed between PM males without FXTAS and controls. Although deficits in information processing speed are unanimously reported in FXTAS samples (Birch et al. 2014), the most comprehensive neuropsychological evaluation of PM males without FXTAS to date (Grigsby et al. 2008) did not detect a significant difference in processing speed between this group and controls. It is possible that this disparity may be due to the difference in ages between these two cohorts; PM males without FXTAS in the study by Grigsby et al. (2008) were older than those included in this report (mean ages 59.1 and 47.8 years, respectively). As onset of FXTAS is typically from the age of 50 years it is possible that the lack of group differences between PM males and controls reported by Grigsby et al. (2008) reflects a healthy survivor effect (i.e. at the time they

**Table 3** Estimated caudate volumes ($mm^3$): Mean (SE)^

| | PM ($n = 13$) | HC ($n = 24$) |
|---|---|---|
| Total | 7020.14 (176.59)* | 7598.69 (127.63) |
| Left | 3374.79 (87.78)** | 3694.85 (63.45) |
| Right | 3645.35 (95.43)* | 3903.84 (68.97) |

^controlling for age and intracranial volume. Brain MRI was contraindicated for two PM males

*$p < .05$; **$p < .01$

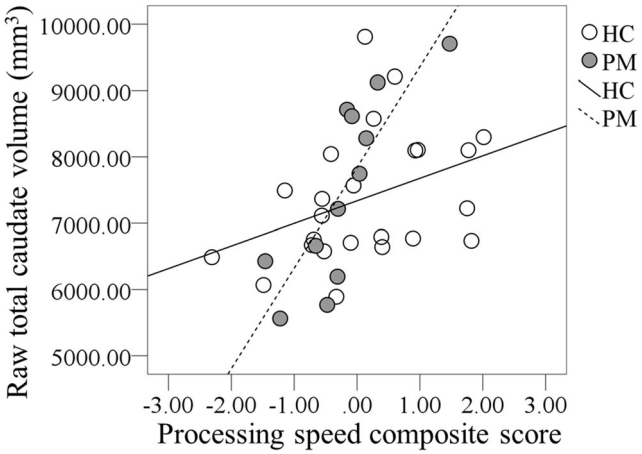


**Fig. 2** Relationship between raw total caudate volume and processing speed composite score in PM males and controls. PM = premutation; HC = healthy controls. Solid and broken lines represent the line of best fit at the subgroup level

were assessed, some older PM males met diagnostic criteria for FXTAS, whereas if they had been assessed at a younger age they would be considered to form part of the 'asymptomatic' group).

A novel finding of this study was that PM males without a diagnosis of FXTAS demonstrated reduced caudate volume compared to controls. This is in contrast to a previous study of subcortical volumes in a slightly smaller ($n = 11$) and older (age range = 47–76 years, mean age = 60.1 years) cohort of PM males without FXTAS (Wang et al. 2013). In the study by Wang et al. (2013), caudate volume was significantly reduced in PM males with FXTAS, but there was no significant difference between PM males without a diagnosis of FXTAS and controls. Again, a potential explanation for the discrepancy in findings is due to the older age of participants in the study by Wang et al. (2013) and a healthy survivor effect. Reduction in caudate volume is one of the earliest and most sensitive biomarkers of neurodegeneration in other degenerative disorders, including Huntington's disease, for which changes in caudate structure are observed in premanifest stages of disease (Domínguez et al. 2013). Early reductions in caudate volume in PM carriers would be consistent with a recent paper suggesting that accelerated trajectories of age-related volume loss in other regions such as the cerebellum and brainstem in PM males begin in young adulthood, well before the onset of FXTAS (Wang et al. 2017). Future studies are needed to determine whether changes in the brainstem, cerebellum and caudate occur independently or as part of the same pathological process.

This study also provides novel evidence of a significant positive association between caudate volume and information processing speed in PM males. This finding is in line with studies of clinical groups including Huntington's disease (Bamford et al. 1995), Parkinson's disease (Price et al. 2016), and multiple sclerosis (Batista et al. 2012), and is consistent with the subcortical cognitive profile attributed to FXTAS (Birch et al. 2014). This suggests that measures of information processing speed provide a marker of subcortical pathology in PM males and could therefore have potential utility for determining risk for FXTAS and/or tracking progression. Executive function was not associated with caudate volume in this sample of PM males in the current study. It is possible that executive dysfunction in PM carriers is better explained by pathology in other brain regions including the cerebellum, corpus callosum (Shelton et al. 2017; Filley et al. 2015) and frontal lobes (Yang et al. 2013).

Our findings did not show any associations between cognitive or neuroimaging measures and CGG repeat length or *FMR1* mRNA levels in PM males. This is in contrast to previous studies in PM males with and without FXTAS (Cornish et al. 2011; Hocking et al. 2012), which suggest poorer cognitive performance among those with larger *FMR1* expansions (particularly over 100 CGG repeats). Rather, our findings are in line with others who have found no significant relationship between *FMR1* molecular measures and either neuropsychological phenotype (Hunter et al. 2008) or subcortical brain volumes (Wang et al. 2013) in PM males. A possible explanation for this discrepancy may relate to differences in the methods of quantifying CGG repeats across independent studies, and their ability to detect mosaicism (Aliaga et al. 2016). Specifically, while there is generally consistency between different PCR based methods in accurate CGG sizing in the premutation range, inconsistencies have been reported for a proportion of PM cases, between PCR based methods and Southern blot analysis for detection on FM alleles on PM allele background (Esposito et al. 2013; Seneca et al. 2012). Another explanation may relate to the distribution of CGG repeat sizes and differences in sample sizes between the studies; within the cohort described in this report, only three PM males had *FMR1* expansions above 100 CGG repeats. Further studies utilising longitudinal study designs with a greater representation of PM males with larger CGG repeats are needed to determine the potential impact of *FMR1* expansion length on cognitive performance and subcortical brain volumes.

There are some limitations of the current study that should be considered. Firstly, the small sample size and cross-sectional study design limit the conclusions that can be drawn from the findings. Future longitudinal studies of cognitive function and caudate volume in PM males are needed to determine whether early reductions in caudate volume and decrements in processing speed may in fact represent an 'at-risk' marker for subsequent progression and development of FXTAS (i.e. as part of a neurodegenerative process), or whether reductions in caudate volume are associated with a neurodevelopmental impact of the PM on brain development.

Further, due to the small sample size, it was not feasible to examine a broader range of cognitive or neuroimaging variables (e.g. thalamus and other basal ganglia volumes) implicated in the pathogenesis of FXTAS (Wang et al. 2013). Another limitation relates to the measurement of total caudate volume, as the small sample size did not allow for analyses of the left and right caudate separately. Similarly, we were not able to undertake specific analyses of the caudate head and body/tail, each of which has unique anatomical connections to select cortical and subcortical structures and may therefore impact different cognitive functions (Robinson et al. 2012). Future imaging studies could utilise a broader range of cognitive and neuroimaging measures, including measures of structural and functional connectivity, to determine whether cognitive changes may arise due to decreased connectivity between key subcortical and cortical regions implicated in higher order cognitive functions. Due to the limited sample size of PM males in the current study and the analyses this would require (e.g. with stringent adjustments for multiple comparisons), the inclusion of additional cognitive and neuroimaging measures was beyond the scope of this report.

In conclusion, our findings provide the first evidence of associations between select cognitive measures and caudate volume in PM males without FXTAS. We have demonstrated that volume loss in the caudate may be associated with cognitive slowing in PM males and that this may be observed prior to the onset of FXTAS. These findings build on an expanding body of work to suggest that cognitive features of FXTAS arise due to pathology within subcortical brain structures involved in cognitive function. If confirmed in future studies with larger PM cohorts, these findings will have important implications for the identification of sensitive measures with potential utility for tracking cognitive decline. Longitudinal studies are required to confirm the extent to which changes in cognitive function and caudate volume in PM males represent an early indicator of vulnerability for decline associated with FXTAS.

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## Compliance with ethical standards

**Conflict of interest** RCB declares that she has no conflict of interest. DRH declares that he has no conflict of interest. WW declares that he has no conflict of interest. NGK declares that she has no conflict of interest. KMC declares that she has no conflict of interest. DEG declares that he has no conflict of interest. CR declares that she has no conflict of interest. JNT declares that he has no conflict of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

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