

Impaired Response Inhibition Is Associated With Self-Reported Symptoms of Depression, Anxiety, and ADHD in Female *FMR1* Premutation Carriers

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Fragile X Mental Retardation 1 (FMR1) premutation carriers (PM-carriers) have a defective trinucleotide expansion on the *FMR1* gene that is associated with continuum of neuropsychological and mental disorders. Currently, little is known about the distinct subcomponents of executive function potentially impaired in female PM-carriers, and there have been no investigations into associations between executive function and incidences of mental disorders. A total of 35 female PM-carriers confirmed by Asuragen triple primed PCR DNA testing and 35 age- and intelligence-matched controls completed tests of executive function (i.e., response inhibition and working memory) and self-reported on social anxiety, depression, and ADHD predominantly inattentive (ADHD-PI) symptoms. Compared to controls, PM-carriers were significantly elevated on self-reported social anxiety and ADHD-PI symptoms. Irrespective of mental symptoms, female PM-carriers performed significantly worse than controls on a response inhibition test, and further investigations revealed significant correlations between executive function performance and self-reported symptoms of anxiety, depression and ADHD-PI. Critically, among PM-carriers with good executive function performance, no women exceeded threshold markers for probable caseness of mental disorder. However, rates of probable caseness were elevated in those with average performance (response inhibition: social anxiety: 41.7%;

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Abbreviations: *FMR1* gene, Fragile X Mental Retardation 1 gene; FMRP, Fragile X Mental Retardation Protein; FXTAS, fragile x-associated tremor/ataxia syndrome; PM-carrier, premutation carrier.

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depression: 20%; ADHD: 44.4%; working memory: social anxiety: 27.3%; depression: 9.1%; ADHD: 18.2%) and highly elevated for those with poor executive function performance (response inhibition: social anxiety: 58.3%; depression: 80%; ADHD: 55.6%; working memory: social anxiety: 100%; depression: 50%; ADHD: 83.3%). These data suggest that subtle executive dysfunction may be a useful neuropsychological indicator for a range of mental disorders previously reported in female PM-carriers. © 2013 Wiley Periodicals, Inc.

Key words: Fragile X Mental Retardation Protein (FMRP); fragile x-associated tremor/ataxia syndrome (FXTAS); attention deficit-hyperactivity disorder (ADHD); depression; anxiety; executive function; premutation; Fragile X Mental Retardation 1 (FMR1)

INTRODUCTION

The *fragile X mental retardation 1* (*FMR1*) gene contains a trinucleotide expansion of a CGG repeat sequence in the 5' untranslated region at the Xq27.3 locus. This gene can be defective and is associated with a continuum of neurodevelopmental, neurodegenerative, and neuropsychological involvement [Jacquemont et al., 2011]. At full expansions of >200 CGG repeats, epigenetic mechanisms "silence" transcription of the *FMR1* allele, and through low production of the Fragile X Mental Retardation Protein (FMRP), this leads to the neurodevelopmental delay and autistic features that are characteristic of fragile X syndrome (FXS) [Cornish et al., 2008a]. In recent years, much research has focused on premutation (PM) expansions of between 55 and 200 CGG-repeats, which can lead to variable, gender-specific phenotypes. For male PM-carriers, research suggests a subtle FXS "signature" of weaknesses in executive function, visuospatial processing and attentional control [Cornish et al., 2005, 2011; Hocking et al., 2012]. In contrast, female PM-carriers show evidence for anxious and depressive symptomatology, subtle problems in executive function, and mild difficulties with mathematical reasoning and inattention [Loesch et al., 2003a; Lachiewicz et al., 2006; Roberts et al., 2009; Hunter et al., 2012a]. However, the presence of a female phenotype is controversial, and there are gaps in our understanding of the executive function deficits that may be associated with the female *FMR1* premutation. Although protective effects from the second X chromosome result in a milder phenotype [Leehey et al., 2008], mental disorders in females may be more prevalent than in male PM-carriers [Hunter et al., 2010], and this emphasizes the importance of identifying neuropsychological indicators of at-risk profiles in female PM-carriers.

Existing studies have shown an age-related deterioration in cognitive, motor and anxiety symptoms [Adams et al., 2010; Narcisa et al., 2011; Sterling et al., 2013], as well as impairments on frontally mediated tasks of processing speed and executive function in female PM-carriers [Yang et al., 2013]. These clinical and behavioral phenotypes may be associated with an increased risk for neurodegenerative decline associated with fragile X-associated tremor/ataxia syndrome (FXTAS). Specifically, approximately 8–16% of females (and 45% males) over the age of 50 go on to develop FXTAS, which is primarily characterized by ataxia and intention

tremor, dementia, mood, and global executive function deficits [Jacquemont et al., 2003; Berry-Kravis et al., 2007; Rodriguez-Revena et al., 2009]. There are also cellular and volumetric changes in FXTAS patients, including the presence of intranuclear inclusion bodies, and widespread cortical and cerebellar structural abnormalities [Greco et al., 2002, 2006; Hashimoto et al., 2011b,c]. Despite the lower prevalence and penetrance of FXTAS in females, there is evidence from post-mortem examinations of an increased risk for *FMR1*-dependent neuro-pathological changes (amyloid plaques and intranuclear inclusion bodies) in older female PM-carriers [Tassone et al., 2012]. Females may also develop fragile X primary ovarian insufficiency (FXPOI), which encompasses irregular menses, fertility problems, hormonal changes and a 20% risk for premature menopause [Sherman, 2000; Wittenberger et al., 2007]. These clinical consequences are thought to result from mRNA gain-of-function toxicity, where over-expression of expanded mRNA transcripts leads to sequestration of RNA binding proteins from their pre-determined role [Tassone et al., 2000; Hagerman et al., 2001; Sellier et al., 2013]. Together these studies indicate synergistic effects of increasing age and *FMR1* molecular events in female PM-carriers well before the presence of more severe age-related decline.

The presence of a cognitive phenotype in adult female PM-carriers is controversial, with standardized neuropsychological tests revealing no evidence for global cognitive decline [Hunter et al., 2008b, 2009; Allen et al., 2011]. For example, when Hunter et al. [2008b] examined performance on standardized tasks of executive function in a large cohort of male and female PM-carriers aged 18–50 years old, PM-carriers performed similarly to controls on all measures. However, a limitation of these previous studies has been the over-reliance on gross neuropsychological tests that tap into multiple cognitive constructs. It is well established that executive function is a multifactorial construct that can be fractionated into separable but not completely independent component processes—that is, mental set-shifting, working memory, and inhibition of prepotent thoughts and behaviors [Miyake et al., 2000; Miyake and Friedman, 2012]. These component processes, which guide and maintain cognitive control- and goal-directed behaviors, are subserved by complex functional links between prefrontal, basal ganglia, and cerebellar neural circuits [Heyder et al., 2004]. Thus impairments in one or more of these component processes may not severely disrupt gross executive functioning [Chan et al., 2008], yet when teased apart they may reveal subtle cognitive profiles that represent the earliest changes in vulnerable neural networks [Christodoulou et al., 2012]. For example, Cornish et al. [2011] showed that in male PM-carriers there were subtle deficits in inhibitory control and executive working memory, beginning as early as middle adulthood, and progressively deteriorating with increasing age and CGG repeat size. There is only limited evidence for a profile of poor executive functioning in adult female PM-carriers, which has revealed specific difficulties in mathematical reasoning and self-regulation of behavior and attention [Loesch et al., 2003a; Steyaert et al., 2003; Lachiewicz et al., 2006]. More recent studies in older female PM-carriers without FXTAS have shown age-related decline in linguistic aspects of organization and planning [Sterling et al., 2013], and frontally mediated impairments in inhibition, working memory, and performance monitoring [Yang et al., 2013]. Given

that the majority of recent studies have been conducted in older PM-carriers, to date little is known about how early changes in specific subcomponents of executive function are associated with other aspects of the distinctive female phenotype.

In addition to emerging evidence for a subtle profile of executive dysfunction, female PM-carriers may suffer from a range of mental disorders including anxiety, depression, and attention deficit-hyperactivity disorder (ADHD) [Franke et al., 1998; Johnston et al., 2001; Roberts et al., 2009; Hunter et al., 2010, 2012a]. Indeed, extant studies have shown that executive dysfunction is frequently comorbid with an ADHD diagnosis [Barkley, 1997; Willcutt et al., 2005]. This may result from a common dysfunction of fronto-subcortical-cerebellar pathways or alterations to transmission in the prefrontal cortex system [Seamans and Yang, 2004; Faraone, 2005]. There is also accumulating evidence to suggest that executive dysfunction is a prevailing characteristic of both anxiety and depression [Ottowitz et al., 2002; Micco et al., 2009; Hosenbocus and Chahal, 2012]. Furthermore, executive function is associated with performance on experimentally based neuropsychological investigations of emotional regulation [Schmeichel et al., 2008; Gyurak et al., 2009] and physiological measures of acute stress reactivity [Hendrawan et al., 2012]. It has been suggested that a disruption of “frontally located” executive functions may actively reduce the inhibition of more posterior emotion systems, resulting in overactive transmission within amygdala and hippocampal regions underlying anxiety and depressive symptoms [Galynker et al., 1998; Ohta et al., 2008; Ray and Zald, 2012]. Taken together with previous evidence for impairments in frontal executive functions in older female-PM carriers [Hashimoto et al., 2011a; Yang et al., 2013], these findings raise the possibility that poorly regulated frontal activation may be concomitantly associated with subtle executive dysfunction and symptoms of mental disorders. Furthermore, in light of recent data showing a later than expected age-of-onset for psychiatric problems in PM-carriers [Seritan et al., 2013], these suggested cognitive and psychiatric changes may well reflect the first signs of more severe age-related neurological change.

In the current study, we investigated for the first time whether distinct subcomponents of executive function are impaired and, if

so, whether executive function deficits are associated with psychological symptoms in adult females with the *FMR1* premutation. In line with our previous investigations of the executive function profile in male PM-carriers [Cornish et al., 2008b, 2009, 2011], we hypothesized that female PM-carriers would show subtle deficits in the areas of inhibition and working memory, resembling in a milder form the executive profile in male PM-carriers. Furthermore, in light of the high rates of behavioral and emotional profiles in female PM-carriers, we expected that specific subcomponents of executive function would be associated with symptoms of ADHD, anxiety, and depression.

METHOD

Study Participants

A total of 35 female PM-carriers aged between 22 and 55 were recruited through support groups and population-based fragile X carrier screening studies [Metcalf et al., 2008]. Female control participants ($n = 35$) aged between 22 and 55 years old were also recruited through population-based fragile X carrier screening studies, and through local networks and via online advertisements. All participants were English speaking with no history of epilepsy or of a serious head injury and had normal (or corrected) vision and hearing, and no sign of color blindness or intellectual disability as assessed using the Wechsler Abbreviated Scale of Intelligence (FSIQ < 70). The female PM-carriers and controls were well-matched on age, IQ, socioeconomic status, and current use of psychotropic medication(s), but female PM-carriers were significantly more likely to be caring for a child with special needs ($P \leq 0.001$). The small portion of medicated women in this study were taking anti-depressants, with two female PM-carriers additionally taking anti-psychotic medications and one PM-carrier additionally taking a stimulant. 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). The descriptive information and statistics are shown in Table I.

TABLE I. Means and Standard Deviations of Sample Characteristics for Female *FMR1* PM-Carriers and Control Participants

	<i>FMR1</i> PM-carriers (N = 35)	Control (N = 35)	
	M ± SD (range)	M ± SD (range)	P-value
Age (years)	41.14 ± 8.34 [22–55]	41.11 ± 8.64 [22–55]	0.989
FSIQ	110.26 ± 10.94 [88–128]	111.91 ± 9.54 [79–129]	0.506
VIQ	106.59 ± 13.90 [73–128]	108.11 ± 11.36 [84–136]	0.619
PIQ	110.86 ± 11.34 [87–133]	113.89 ± 11.15 [79–133]	0.260
Socioeconomic disadvantage [% < AUD \$51,999]	8.6%	14.3%	0.869 ^a
Use of psychotropic medications [% yes]	14.3%	5.7%	0.232 ^a
Child special needs [% yes]	65.7%	17.1%	<0.001 ^{a,**}
CGG-repeat length	86 ± 15.07 [59–122]	26 ± 3.52 [20–42]	<0.001 ^{**}

FSIQ, Full Scale Intelligence Quotient; PIQ, Performance Intelligence Quotient; SD, standard deviation; VIQ, Verbal Intelligence Quotient.

^aChi square test for independence.

^{**} $P < 0.01$.

Molecular Analyses

To ascertain CGG repeat size, DNA was extracted from 2 ml whole blood from all participants using the Promega Maxwell® 16 Instrument and associated Maxwell® 16 Blood DNA Purification Kit (Promega, Maddison, WI; Cat No.: AS1010). PCR was performed using the Asuragen® AmpliX FMR1 PCR Kit as this assay has been shown to detect a full range of fragile X expanded alleles [Chen et al., 2010]. PCR products were assessed via capillary electrophoresis on an Applied Biosystems 3130 Genetic Analyzer (Life Technologies, Carlsbad, CA) with electropherogram analysis conducted using GeneMapper® software. All procedures were performed in accordance with manufacturer's instructions.

MEASURES

Neuropsychological Tests

The following tests of executive function were selected on the basis of the age- and CGG-repeat vulnerability profile in male PM-carriers [Cornish et al., 2011]: Hayling Sentence Completion Test, Stroop Color and Word Test, and Letter-Number Sequencing.

Hayling Sentence Completion Test. The *Hayling Test* [Burgess and Shallice, 1997] involves a sentence completion task in which participants firstly have to complete sentences with a related or connected word that is meaningful to the sentence (Section A), and secondly (Section B) complete sentences with words that are unconnected to the sentence. The latter requires inhibiting a prepotent response that has been previously established. The second section (i.e., unconnected completion) of the Hayling Test was scored for Category A (connected) and Category B (somewhat connected) errors, yielding a converted A + B error score. A higher score indicated a greater number of errors and worse performance.

Stroop Color and Word Test [Golden and Freshwater, 2002]. The Stroop is based on the principle that a participant must respond to the color of the word whilst selectively inhibiting the more automatic response of reading the printed word. Performance was determined by the number of correctly named words within a 45 sec timeframe and the calculated Stroop Interference score, in which a negative value indicated an interference effect, was taken for further analyses.

Letter-Number Sequencing (LNS) Test. The LNS is a subtest from the Wechsler Adult Intelligence Scale-IV (WAIS-IV) and is designed to assess the participant's ability to temporarily store and manipulate information. Participants listened to a combination of letters and numbers of increasing lengths, and were required to repeat each letter-number sequence, however with the numbers in ascending order followed by the letters in alphabetical order. The scores from the LNS were calculated after three consecutive trial failures on a given level, with the total score calculated by adding all correct items. LNS scores 1 SD below the group mean were indicative of poor performance.

Behavioral Measures of Psychological Symptoms

The following self-report questionnaires were selected on the basis of their sensitivity to psychological symptoms previously reported

in female PM-carriers [Hunter et al., 2010]: The self-report Liebowitz Social Anxiety Scale (SR-LSAS), Depression Anxiety Stress Scales (DASS), and Brown Attention Deficit Disorder Scales (Brown ADD).

The SR-LSAS is a widely used 24-item Likert-scale self-report questionnaire that measures the impact of *social anxiety* symptoms in the preceding week across a range of social situations adapted from day-to-day life. Based on a clinician's administered Liebowitz Social Anxiety Scale (CA-LSAS), the SR-LSAS has excellent psychometric properties including high internal consistency (0.94), high convergent validity with the CA-LSAS, and discriminant validity for social anxiety [Liebowitz, 1987; Fresco et al., 2001; Rytwinski et al., 2009]. Caseness for social anxiety is indicated by a score >50 and can be classified as moderate (50–65), marked (65–80), severe (80–95), or extremely severe (>95).

To assess symptoms of *depression* we administered the DASS [Lovibond and Lovibond, 1995], a 42 item self-report questionnaire that measures the frequency and severity of anxiety, depression, and stress experienced during the preceding week. The psychometric properties of the DASS are good, with high internal consistency for the subscales depression (0.96), anxiety (0.92), and stress (0.95) alongside adequate reliability, and excellent convergent validity and discriminant validity [Crawford and Henry, 2003; Page et al., 2007]. We examined scores on the depression sub-scale only. A score of greater than 10 indicated caseness for depression, and the degree of depression was indexed as mild (10–13), moderate (14–20), severe (21–27), or extremely severe (28+).

To measure behavioral ADHD symptoms, we administered the adult Brown ADD scale (18+ years), a 40 item self-report questionnaire that assesses the impact of inattentive behavioral symptoms over the preceding 6 months. This scale scores high for internal consistency reliability (0.96) and has excellent specificity for ADHD [Brown, 1996; Muniz, 1996; Rucklidge and Tannock, 2002]. The term ADD has been re-classified as ADHD-Predominantly Inattentive (ADHD-PI) since the creation of this scale, and thus it was deemed appropriate to interpret data from this scale as indicative of cognitive and affective symptoms associated with the inattentive criterion of ADHD (i.e., ADHD-PI). We selected the total score and used it for ADHD-PI determination of caseness by examining the Threshold Interpretation Scale (e.g., ADHD-PI possible but not likely: 0–40; ADHD-PI probable but not certain: 40–55; ADHD-PI highly probable: 55–120).

STATISTICAL ANALYSES

Data were analysed using IBM SPSS Statistics 20.0. Normality was checked with the Shapiro–Wilk test. We first conducted independent *t* tests to compare group differences for raw scores on the neuropsychological assessments of executive function and self-reported psychological symptoms. Further comparisons of executive function performance were conducted after excluding those participants meeting threshold for caseness for probable mental disorder. Between group comparisons of executive function performance and psychological symptoms were further analyzed after removing participants caring for a child with special needs. However, given unequal numbers of participants aged over 40 and not caring for a child with special needs (PM-carriers = 2;

controls = 15), we compared only women below the age of 40 where numbers were relatively equal (PM-carriers = 10; controls = 14). This approach ensured comparable groups and reduced confounding effects due to age. To mark thresholds for neuropsychological involvement, we converted Hayling error scores to scaled scores (range 1–8, with a score of 1 marking impaired performance) so that a scaled score between 4 and 1 categorically signified “poor” performance. Similarly, a negative Stroop Color Word Interference Score indicated interference. Threshold markers for working memory dysfunction were not included in the task, and thus we marked all participants performing less than 1 SD from the mean as having “poor” working memory performance. Using Chi square test for independence, we further compared PM-carriers and controls on percentages of caseness for a probable mental disorder as defined by threshold criterion markers within self-report scales. This was repeated for a self-reported lifetime diagnosis (any previous diagnosis) of depression, anxiety and ADHD. Correlational analyses with Pearson’s coefficients were conducted between executive function performance, psychological symptoms, age, and CGG-repeat length. Finally, to examine the percentage of our PM-carrier cohort meeting threshold for caseness (i.e., those with probable anxiety, depression, or ADHD-PI) as a function of executive function performance, we stratified percentages of PM-carrier women meeting threshold for probable caseness by executive function impairment. A Bonferroni correction across each domain (i.e., executive function and psychological symptoms) allowed for a more conservative P value ($P < 0.017$) for all analyses.

RESULTS

Neuropsychological Tests of Executive Function and Self-Reported Symptoms of Social Anxiety, Depression, and ADHD-PI

As evident in Table II, between group comparisons reveal that when compared to controls, the PM-carriers were comparable on Stroop

interference and working memory performance on LNS, but showed significantly poorer response inhibition as measured by errors on the Hayling Test ($P \leq 0.001$). After excluding those participants meeting criteria for caseness for probable mental disorder, the differences in response inhibition between PM-carriers and controls did not survive Bonferroni correction ($t(49) = 2.390$, $P = 0.023$). Similarly, after excluding those women caring for children with special needs, the poorer response inhibition in PM carriers relative to controls did not reach significance after Bonferroni correction ($t(22) = 2.137$, $P = 0.044$).

With regard to levels of self-reported behavioral problems, there were no significant differences between groups for self-reported depression, but levels of both social anxiety ($P = 0.023$) and ADHD-PI ($P = 0.005$) were elevated in PM-carriers compared to controls. Further analyses with participants *not* caring for a child with special needs revealed increased behavioral problems in PM-carrier women compared to controls for social anxiety (PM-carrier: 43.70; control: 35.50), depression (PM-carrier: 2.70; control: 2.43), and ADHD-PI (PM-carrier: 40.30; control: 25.57); however, these group differences were not statistically significant (LSAS: $t(22) = 0.939$, $P = 0.366$; DASS: $t(22) = 0.185$, $P = 0.855$; ADHD-PI: $t(22) = 1.374$, $P = 0.183$).

Chi-square test for independence (with Yates Continuity Correction) revealed that in comparison to controls, there was a higher proportion of PM-carriers with poor response inhibition (PM-carrier: 31.4%; control: 8.6%; $\chi^2(1, n = 70) = 4.375$, $P = 0.036$, $\phi = 0.286$) and caseness for social anxiety (PM-carrier: 34.3%; control: 11.4%; $\chi^2(1, n = 70) = 3.970$, $P = 0.046$, $\phi = 0.272$), but the group differences did not survive adjustment for multiple testing (see Table III).

The proportion of PM-carriers meeting threshold criteria for Stroop Interference, poor working memory, caseness for depression and ADHD-PI did not exceed that observed for control participants. When compared to control participants, PM-carriers were not significantly more likely to self-report a lifetime diagnosis

TABLE II. Means and Standard Deviations for Raw Scores on Neuropsychological Assessments of Executive Function and Self-Report Scales for PM-Carriers and Control Participants

	FMR1 PM-carrier (N = 35)	Control (N = 35)	
	M ± SD [range]	M ± SD [range]	P-value
Executive function			
Hay	10.49 ± 10.26 [0 to 44]	4.0 ± 6.93 [0 to 38]	<0.001**
Stroopl	5.89 ± 12.76 [−10.70 to 47.06]	4.99 ± 7.18 [−10 to 20.87]	0.719
LNS	12.60 ± 3.47 [5 to 20]	13.89 ± 3.21 [9 to 21]	0.112
Self-report scale			
LSAS	46.34 ± 28.53 [6 to 106]	33.03 ± 17.90 [4 to 74]	0.023
DASS_D	3.97 ± 5.70 [0 to 21]	2.37 ± 3.66 [0 to 20]	0.067
ADHD-PI	38.23 ± 27.80 [1 to 101]	22.34 ± 16.21 [0 to 66]	0.005*

ADHD-PI, ADHD-Predominantly Inattentive from the Brown ADD scale; DASS_D, Depression subscale from the Depression Anxiety Stress Scales; Hay, Hayling A + B error score; LSAS, Liebowitz Social Anxiety Scale; LNS: Letter Number Sequencing; SD, standard deviation; Stroop I, Stroop Interference.

Higher scores for LSAS, DASS_D, ADHD-PI, and Hayling’s errors reflect an increase in symptoms and worse performance. Alternatively, higher scores on the Stroop Interference measure and LNS suggest better performance.

* $P < 0.017$.

** $P < 0.001$.

TABLE III. Chi Square Test for Independence Comparing Percentages of PM-Carrier and Control Participants With Poor Performances on Executive Function Tests and Probablecaseness for a Mental Disorder

	PM-carrier (N = 35)	Control (N = 35)	Phi coefficient	Chi square	P-value
	Number (%)	Number (%)			
Poor performance on neuropsychological test					
Inhibitory dysfunction likely	11 (31.4%)	3 (8.6%)	0.286	4.375	0.036
Interference likely	10 (28.6%)	9 (25.7%)	0.032	0	0.100
Working memory problems likely	6 (17.1%)	4 (11.4%)	-0.082	0.117	0.733
Threshold for probable caseness met					
ADHD-PI highly probable	9 (25.7%)	3 (8.6%)	0.227	2.514	0.113
Social phobia probable	12 (34.3%)	4 (11.4%)	0.272	3.970	0.046
Depression probable	5 (14.3%)	0 (0%)	0.277	3.446	0.063
Lifetime diagnosis of a mental disorder (SR)					
ADHD ^a	0 ^a	0%	—	—	—
Anxiety ^b	31.4%	22.9%	0.096	0.650	0.420
Depression ^b	37.1%	25.7%	0.123	1.061	0.303

SR, self-report.

^aChi square test could not be performed due to zero frequency of PM-carrier ADHD diagnoses.

^bFurther comparisons of proportions of a lifetime diagnosis between PM-carrier women and Australian statistics [any anxiety disorder: 18% women; any affective disorder (i.e., depression): 7.1% women] show significant elevations in diagnostic rates for the presently examined PM-carriers [anxiety: χ^2 (1, n = 35) = 4.276, P = 0.039; depression: χ^2 (1, n = 35) = 47.893, P = 0.001]. In contrast, the proportion of lifetime diagnoses in our control group was comparable to Australian statistics for anxiety [χ^2 (1, n = 35) = 0.559, P = 0.454], yet elevated for depression [χ^2 (1, n = 35) = 18.386, P = 0.001].

(any previous diagnosis) of anxiety (31.4%; χ^2 (1, n = 70) = 0.096, P = 0.420) or depression (37.1%; χ^2 (1, n = 70) = 1.061, P = 0.303). Given that these percentages from controls may not be reflective of true caseness in a general population, we further compared proportions of a lifetime diagnosis between PM-carrier women and Australian statistics (ABS: National Survey of Mental Health and Wellbeing) to show significant elevations in diagnostic rates for PM-carriers in the present cohort (anxiety: χ^2 (1, n = 35) = 4.276, P = 0.039; depression: χ^2 (1, n = 35) = 47.893, P = 0.001). In contrast, the proportion of lifetime diagnoses in our control group were comparable to Australian statistics for anxiety (χ^2 (1, n = 35) = 0.559, P = 0.454), but were elevated for depression (χ^2 (1, n = 35) = 18.386, P = 0.001). Furthermore, a comparable percentage of women with and without children

with special needs reported a lifetime diagnosis of depression (with: 39.1%; without: 33.3%) and anxiety (with: 30.4%; without: 33.3%). With regard to ADHD, despite elevated rates of probable ADHD-PI in female PM-carriers (25.7%), the medical history questionnaire showed that no women in this study had previously received a medical diagnosis of ADHD-PI.

Associations Between Executive Function Performance and Self-Reported Symptoms of Social Anxiety, Depression, and ADHD-PI

The associations between performance on tests of executive function and self-reported psychological symptoms were examined through correlational analyses. As shown in Table IV, there were

TABLE IV. Correlational Associations Between Self-Reported Symptoms of a Mental Disorder and Performance on Neuropsychological Assessments of Executive Function for FMR1 PM-Carriers and Controls

	PM-carrier (N = 35)			Control (N = 35)		
	Hay	Stroop-I	LNS	Hay	Stroop-I	LNS
LSAS	0.440*	0.089	-0.619**	0.092	-0.055	0.160
DASS_D	0.627**	-0.020	-0.377	-0.253	-0.010	-0.178
ADHD-PI	0.368	0.264	-0.496*	-0.258	-0.149	-0.038

DASS_D, Depression subscale from the Depression Anxiety Stress Scales; Hay, Hayling's Test; LSAS, Liebowitz Social Anxiety Scale; LNS, Letter Number Sequencing; SD, standard deviation; Stroop-I, Stroop Interference.

Partial correlation controlling for use of medications with a Bonferroni corrected P -value of 0.017 selected. Higher scores for LSAS, DASS_D, ADD-PI, and Hayling's errors reflect an increase in symptoms and worse performance. Alternatively, higher scores on the Stroop Interference measure and LNS suggest better performance.

* P < 0.017.

** P < 0.001.

several significant correlations between executive function performance and self-reported symptoms in PM-carriers. After controlling for medication use, performance as indexed by errors on the Hayling and working memory performance on LNS were significantly correlated with elevated levels of social anxiety (Hayling: $r = 0.440$, $P = 0.009$; LNS: $r = -0.619$, $P \leq 0.001$), depression (Hayling: $r = 0.627$, $P \leq 0.001$), and ADHD-PI (LNS: $r = -0.496$, $P = 0.003$). Associations between both symptoms of depression and working memory performance ($r = -0.377$, $P = 0.028$) and symptoms of ADHD-PI and inhibitory control ($r = 0.368$, $P = 0.032$) did not survive the Bonferroni correction. No significant correlations between scores on self-report scales and the Stroop Interference task were observed, nor were there correlations between neuropsychological performance and self-reported symptoms for controls with normal alleles.

Likelihood of Caseness for a Mental Disorder Stratified by Executive Function Profile

To determine which threshold levels of executive dysfunction were most associated with caseness for a mental disorder, we stratified the proportion of individuals meeting probable caseness for social anxiety, depression and ADHD-PI by their executive function profile (see Table V). This analysis showed that caseness was completely absent in those with excellent Hayling Test and LNS performances. In contrast, rates of behavioral problems were moderately elevated in those with average performance on both the Hayling Test (social anxiety: 41.7%; depression: 20%; ADHD-PI: 44.4%) and LNS (social anxiety: 27.3%; depression: 9.1%; ADHD-PI: 18.2%). Finally, psychological symptoms were very highly elevated for those with poor performance on the Hayling

Test (social anxiety: 58.3%; depression: 80%; ADHD-PI: 55.6%) and LNS (social anxiety: 100%; depression: 50%; ADHD-PI: 83.3%). Stroop performance was not sensitive to caseness for a mental disorder.

Correlations Between Age/CGG-Repeat Length and Executive Function/Self-Reported Psychological Symptoms

Correlational analyses showed that there were no significant associations between CGG-repeat length and performance on tests of executive function and self-reported behavioral symptoms. The correlations between increasing age and poorer performance across the neuropsychological tests of executive function (Hayling Test: $r = 0.357$, $P = 0.035$; Stroop Interference task: $r = -0.383$, $P = 0.023$; LNS: $r = -0.327$, $P = 0.055$) did not reach significance after the Bonferroni correction (see Table VI).

DISCUSSION

In this study we investigated the utility of executive function profiles as neuropsychological indicators of symptoms of psychological disorders in females with the *FMR1* premutation. First, our results showed elevations in self-reported symptoms of social anxiety (34.3%) and ADHD-PI (25.7%), alongside core impairments in response inhibition. As expected, poor executive functions (both in response inhibition and working memory) were strongly associated with self-reported symptoms of mental disorders for female PM-carriers which differentiated them from controls with normal alleles. Further analysis revealed that probable caseness for a mental disorder was most common amongst female PM-carriers that performed poorly on neuropsychological tests of executive function, but PM carriers with preserved executive function were relatively risk-free from psychological symptoms. This suggests

TABLE V. Proportion of PM-Carriers Meeting Criteria for Probable Caseness for a Mental Disorder Stratified by Executive Function Profile

	Probable social anxiety (%)	Probable depression (%)	Probable ADHD-PI (%)
Hayling Test ^a			
Poor (N = 11)	58.3	80.0	55.6
Average (N = 16)	41.7	20.0	44.4
Excellent (N = 8)	0	0	0
Stroop Inhibition ^b			
Interference (N = 10)	41.7	20	22.2
No Interference (N = 25)	58.3	80	77.8
Letter number seq. ^c			
Poor (N = 6)	100	50	83.3
Average (N = 22)	27.3	9.1	18.2
Excellent (N = 7)	0	0	0

^aThreshold determinant: poor = scaled score 1–4; average = scaled score 5–6; excellent = scaled score 7–8.

^bThreshold determinant: Interference = score <0; No interference = score >0.

^cThreshold determinant: poor = 1 SD or more below the mean; average = from 1 SD below mean to 1 SD above mean; excellent = 1 SD or more above mean.

TABLE VI. Correlational Associations Between Both Age and CGG Repeat Length With Self-Reported Behavioral Symptoms and Performance on Neuropsychological Assessments of Executive Function for *FMR1* PM-Carriers and Controls

	PM-carrier		Control	
	CGG-length	Age	CGG-length	Age
Hay	0.178	0.357	−0.098	0.154
Stroop-I	−0.107	−0.383	−0.059	−0.223
LNS	−0.142	−0.327	0.177	0.053
LSAS	−0.040	0.168	−0.181	−0.268
DASS_D	0.050	0.147	0.170	−0.246
ADHD-PI	−0.032	−0.047	0.028	−0.241

ADHD-PI, ADHD-Predominantly Inattentive; DASS_D, Depression subscale from the Depression Anxiety Stress Scales; Hay, Hayling's Test; LSAS, Liebowitz Social Anxiety Scale; LNS, Letter Number Sequencing; SD, standard deviation; Stroop-I, Stroop Interference.

Higher scores for LSAS, DASS_D, ADD-PI, and Hayling's errors reflect an increase in symptoms and worse performance. Alternatively, higher scores on the Stroop Interference measure and LNS suggest better performance.

that in adult female PM-carriers, executive function may tie in a range of symptoms of psychological disorders including social anxiety, depression and ADHD-PI, with the likelihood of involvement decreasing as a function of executive function ability. These findings have important clinical implications as neuropsychological tests of executive function could identify probable caseness for symptoms of psychological disorders in adult female PM-carriers.

The poorer performance on the Hayling Test indicated a core inhibitory control problem even after excluding women with a probable mental disorder and carer burden associated with raising a child with special needs. This is consistent with our previous studies showing inhibitory control deficits in male PM-carriers [Cornish et al., 2008b, 2011], and suggests a general *FMR1* premutation deficit in overcoming habitual word association responses. This implies that the earliest molecular events associated with the expanded CGG sequence (i.e., RNA toxicity, reductions of FMRP) may be domain-specific, with vulnerability only in specific neural circuits. Crawford and Henry [2005] showed that Hayling's test performance is more specific for suppression/inhibition in anterior lesion cases than for posterior lesion cases in brain injured patients. In line with this, Hayling's Test performance correlated with gray matter atrophy of the orbitofrontal cortex in patients with frontotemporal dementia [Hornberger et al., 2011]. This is consistent with findings of reduced prefrontal activation during performance of executive working memory tasks in male PM-carriers [Hashimoto et al., 2011a; Yang et al., 2013], and reduced functional connectivity between prefrontal and more posterior brain regions during memory encoding [Hashimoto et al., 2011c; Wang et al., 2012; Battistella et al., 2013]. These neural alterations may provide an explanation for the association between executive function and psychological symptoms reported here in female PM-carriers. We have previously suggested that selective executive deficits in inhibitory control and working memory may reflect early signs of toxicity to frontal regions in male PM-carriers [Cornish et al., 2011]. Although executive working memory does not appear to be a relative weakness in female PM-carriers, our results suggest frontally mediated inhibitory control impairments may be a core feature of the phenotype in at least a subgroup of at-risk women with the premutation.

The current findings of detected rates of probable caseness for mental disorders in female PM-carriers were relatively comparable to those suggested in previous studies. For example, we report that 34.3% of our participants met threshold markers within the LSAS scale for probable social anxiety (31.4% self-reported a previous clinical diagnosis), while previous studies using different measures of anxiety have documented involvement at 20.9% [Hunter et al., 2008a], 30% [Lachiewicz et al., 2010], and 29.03% [Roberts et al., 2009]. Similarly, while we report that 14% of participants met criteria for probable depression on the DASS (37.1% self-reported a previous clinical diagnosis), other studies using different scales for depression suggest prevalence rates of 26.3% [Hunter et al., 2008a], 33% [Lachiewicz et al., 2010], and 47.3% [Roberts et al., 2009]. Although our findings showed no participants reported a previous clinical diagnosis of ADHD, as many as 25% of female PM-carriers exceeded the threshold marker for highly probable ADHD-PI. This prevalence rate far exceeds a previously reported proportion of ADHD involvement (4.5%) based on an American female PM-

carrier sample [Hunter et al., 2010]; however, it is consistent with neuropsychological investigations showing impaired attentional control in female PM-carriers [Loesch et al., 2003b; Steyaert et al., 2003]. Given that ADHD-PI in women is under-recognized in the general population [Biederman et al., 2002], it is entirely conceivable that female PM-carriers with clinical levels of ADHD-PI remain undiagnosed which may be associated with an increased risk for anxiety disorders and depression [Barkley and Brown, 2008].

The considerable variability in women meeting the threshold for a probable mental disorder is another important finding of the current study. One explanation for heterogeneity in psychological symptoms might be the greater carer burden associated with rearing a child with special needs [Abbeduto et al., 2004]. However, the current findings showed elevated levels of psychological symptoms even in PM-carrier women *not* caring for a child with special needs. Alternatively, other molecular events such as increased mRNA levels and moderately reduced FMRP may play an important role in the variable expression of the psychiatric phenotype in female PM-carriers. With regard to CGG repeat length, we found no relationships with executive functioning and self-reported psychological symptoms. This is consistent with studies suggesting elevated depressiveness in women with both high (>100) and low (<100) CGG repeats [Johnston et al., 2001; Roberts et al., 2009; Seltzer et al., 2012], and lack of association with social anxiety [Adams et al., 2010]. We speculate that a complex range of factors may contribute to increased risk for symptoms of mental disorders in female PM-carriers, involving residual genetic factors, lifetime experiences, hormones, child behavior, and marital satisfaction [Abbeduto et al., 2004; McCarthy et al., 2006; Hunter et al., 2010, 2012b; Seltzer et al., 2012]. We contend that significant associations between executive functions and psychological symptoms provide support for both at-risk profiles in some female PM-carriers, and in a subgroup with preserved executive functioning, some protective effects resulting in a much lower risk for a mental disorder.

A limitation of this research is the correlational nature of the impact of executive function impairments on psychological symptoms detected in female PM-carriers. Prospective longitudinal studies should be conducted to determine whether the observed relationships may be mediated by other factors, since correlations are insufficient to determine the direction of causality between executive function and mental disorders. A second limitation is the use of self-report measures of anxious and depressive symptomatology; however, it should be acknowledged that our conclusions are strengthened by consistency between self-report scales, rates of lifetime diagnoses and prevalence rates reported in previous studies. Future studies should include more detailed clinical interviews such as the Structured Clinical Interview for DSM-IV-TR (SCID) to confirm these relationships in larger samples of female PM-carriers. Future studies would also need to consider variations in residual polygenic effects previously shown to be associated with carer-stress, and symptoms of depression and anxiety [Hunter et al., 2012b; Seltzer et al., 2012]. Finally, this cross-sectional design will need to be extended to a larger sample and follow-up longitudinal analyses to ascertain the lifetime impact of executive dysfunction and symptoms of mental disorders in the same cohort of *FMR1* premutation carriers.

In conclusion, this is the first study to examine neuropsychological indicators of at-risk profiles associated with symptoms of mental disorders in females with *FMR1* premutation. The present data, showing significant associations between psychological symptoms and executive function profiles, may have important clinical implications for the assessment of female PM-carriers at-risk for more severe anxious and depressive symptomatology. Prospective longitudinal studies will be important in determining whether early problems within the frontally mediated networks that subserve response inhibition lead to increased risk for a range of symptoms associated with mental disorders. Follow-up studies will be critical for the development of sensitive neuropsychological markers to identify those female PM-carriers at greatest risk of developing a range of mental disorders across the lifespan.

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