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High Rates of Comorbid Depressive and Anxiety Disorders Among Women with Premutation of the FMR1 Gene

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Abstract

Phenotypic variations are emerging from investigations of carriers of the fragile X mental retardation 1 (FMR1) premutation gene (55 to 200 CGG repeats). Initial studies suggest elevated psychiatric and reproductive system dysfunction, but have largely used self-reports for assessment of psychiatric history. The present study used diagnostic psychiatric interviews and assessed reproductive and menstrual history in women with FMR1 pre-mutation. History of psychiatric diagnoses and data on reproductive functioning were collected in 46 women with FMR1 premutation who were mothers of at least one child with the fragile X full mutation. Results showed a significantly earlier age of menopause (mean age = 45.6 years) relative to the national average age of menopause (mean age = 51 years) and a high rate (76%) of lifetime depressive or anxiety history, with 43% of the overall sample reporting a comorbid history of both diagnoses. Compared to those free of psychiatric history, significantly longer premutation length was observed among women with psychiatric history after adjusting for age, with comorbid women having the highest number of CGG repeats (mean = 95.8) compared to women free of psychiatric history (mean = 79.9). Psychiatric history did not appear significantly related to reproductive system dysfunction, though results may have been obscured by the high rates of psychiatric dysfunction in the sample. These data add to the growing evidence base that women with the FMR1 premutation have an increased risk of psychiatric illness and risk for early menopause. Future investigations may benefit from inclusion of biochemical reproductive markers and longitudinal assessment of psychiatric and reproductive functioning.

Keywords

anxiety; depressive disorders; FMR1 premutation; menopause; women

INTRODUCTION

Fragile X syndrome (FXS), the most common known etiology for heritable intellectual developmental disability (IDD) [Garber et al., 2008], is caused by mutations to the fragile X mental retardation 1 (FMR1) gene located on the X chromosome. An expansion of more

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than 200 CGG repeats in the 5' region of this gene, results in hypermethylation and consequent loss or absent production of FMRP, the protein product of the gene [Verkerk et al., 1991]. Large numbers of trinucleotide repeats (i.e., >200) are commonly referred to as the “full mutation” range, while an expansion of 55 to 200 CGG repeats is referred to as the “premutation” range. In a recent study of FMR1 premutation in the general population, prevalence for women was found to be approximately 1 in 151 women, and 1 in 35 women for the “gray zone,” as defined by 45–54 CGG repeats [Seltzer et al., 2012].

Distinct phenotypic variations in FMR1 premutation are increasingly suggested by investigations of FMR1 premutation carriers [Pembrey et al., 1985; Bourgeois et al., 2011]. Among women, in particular, pathophysiological phenomena observed include depression and anxiety [Johnston et al., 2001; Lachiewicz et al., 2010], fragile-X-associated tremor/ataxia [Berry-Kravis et al., 2007], and reproductive system dysfunction, such as unusual hormonal changes and premature ovarian insufficiency (POI) [Rebar, 2009]. Notably, premature ovarian failure, characterized by menopause before the age of 40, affects nearly 25% of women with the premutation, while it occurs in less than 1% of the typical (non-premutation) female population [Welt et al., 2004]. Women with the FMR1 premutation also report perimenopausal symptoms at earlier ages compared to their peers, and data suggest that they undergo menopause about 5 years earlier, on average [Sullivan et al., 2005]. The pathophysiology of this reproductive system dysfunction in women with the FMR1 premutation is not fully understood. However, across studies there is significant evidence of hormonal irregularities in women with the premutation, such as lower levels of anti-Müllerian hormone, inhibin B, inhibin A, and P4 levels [Welt et al., 2004; Rohr et al., 2008]. Given that perimeno-pause and menopause are associated with increases in psychiatric morbidity [De Caro et al., 2008], and risk for depression in women increases around menopause [Soares and Maki, 2010], reproductive, and hormonal dysfunction in women with FMR1 premutation may be mechanistically related to increased vulnerability for mood disorders in this population [Rodriguez-Revenga et al., 2008]. Compounding consideration of the potential association of increased risk of psychiatric and reproductive system dysfunction is the stress associated with caregiving to children with developmental disabilities [Roberts et al., 2009].

Notably, in the few available studies to date on psychiatric dysfunction in women with the FMR1 premutation, most have assessed psychiatric history using self-report rather than DSM-IV based diagnostic interviews, and few have included control groups. Three studies that compared premutation carriers to control groups consisting of mothers of children with non-FXS IDD found differing results [Reiss et al., 1993; Rodriguez-Revenga et al., 2008]. Specifically, an early study that used diagnostic interviews in premutation-range mothers of children with FXS and unaffected mothers of non-FXS children with intellectual and developmental disabilities found elevated rates of depressive and anxiety disorders relative to national averages, but no particular differences in rates among either group [Reiss et al., 1993]. Another study by Franke et al. [1998] found a higher rate of social phobia, but no other Axis I disorders, among premutation-range mothers of FXS children compared to a control group of mothers of non-FXS autistic children. In contrast, results from a later study that used self-report measures in FMR1 premutation carriers mothers of children with FXS, and non-carrier mothers of children with non-FXS IDD, and mothers from the general

population, showed a greater risk of psychiatric problems in both groups of mothers with IDD-affected children, but an even greater tendency toward depression among FMR1 premutation carriers [Rodriguez-Revenge et al., 2008]. Several other investigations have reported elevated rates of clinically diagnosed [Roberts et al., 2009; Bourgeois et al., 2011] and self-reported symptoms of depression and anxiety in women with FMR1 premutation compared to the general population [Johnston et al., 2001; Hessler et al., 2005; Hunter et al., 2010].

Five studies to date have investigated the relationship of CGG repeat length to psychiatric features in females with the FMR1 premutation, and only one of these investigations included a DSM-IV based diagnostic interview. One study showed a positive association between self-reported depressive symptom severity and pre-mutation length [Johnston et al., 2001], while a later epidemiological study that included diagnostic interviews found an increased likelihood of major depressive disorder (MDD) with shorter premutation length [Roberts et al., 2009]. None of the other three studies, two of which used self-reported measures [Thompson et al., 1994; Hessler et al., 2005] and one that used the Diagnostic Interview Genetic Studies [Franke et al., 1998], found any relationship between CGG length and depressive symptoms [Hessler et al., 2005] or MDD [Thompson et al., 1994; Franke et al., 1998].

Aside from the current investigation, limited data exist with respect to concurrent psychiatric and reproductive history in women with FMR1 premutation. To our knowledge, there is only one report by Hunter et al. [2010], which reported an association between self-reported symptoms of depression and anxiety and presence of symptoms of ovarian insufficiency, as evidenced by menopause or irregular menstrual cycles. The present study is the first to our knowledge to use formal clinical interviews to characterize both psychiatric history and menstrual and reproductive history in women with the FMR1 premutation.

MATERIALS AND METHODS

All subjects were women who carried the FMR1 premutation gene (i.e., between 55 and 200 CGG repeats on the FMR1 gene) and were recruited from families in a larger research study of children with FXS and their unaffected siblings (R01-MH050047, PI: Reiss). In that study, families were eligible if they had at least one child with FXS and one same sex, unaffected sibling between the ages of 6 and 17 years old at the time of recruitment (N = 75). At the time of recruitment of each family into the larger study, mothers were tested for general intelligence using the Wechsler Adult Intelligence Scale-III [WAIS-III; Corporation, 1997], as well as FMR1 premutation length using an established Southern blot and polymerase chain reaction (PCR) analyses followed by FMR1-specific probe hybridization [Oberle et al., 1991]. All 75 FMR1 premutation carrier mothers from the larger study received a one-time mailed invitation to participate in a study concerning reproductive health and mood, to which 48 women replied (46 who were interviewed and 2 who declined participation). No differences were observed between women who replied compared to those who did not reply to the one-time mailing with respect to age, number of children, IQ, or years of education (data available upon request). The mean age of the 46 women included in

the final sample was 47.7 years ($SD = 5.6$, range = 28–56) and their mean IQ was 104.5 ($SD = 13.9$, range = 80–139).

The study was approved by the Stanford University Human Research Institutional Review Board. Written informed consent was obtained from all study participants prior to any data collection. All participants underwent the Structured Clinical Interview for the DSM–IV [SCID; First et al., 1997] by a trained clinical interviewer either in-person (56.5%) or by telephone following the in-person visit to Stanford (43.5%). Participants were also asked about their reproductive history, lifetime, and current pattern of menstruation (e.g., frequency, regularity, and recency), use of hormonal therapies (e.g., birth control and hormonal replacement), current medications and supplements, and general medical history.

Statistical analysis was conducted using SPSS version 19. Pearson correlations, t-tests, and analysis of variance (ANOVA) and covariance (ANCOVA) were used to test for associations between psychiatric history, premutation length, and menopause-related variables, with age as a covariate in all ANCOVA models. Chi-square tests were used to assess for differential distribution of disorders and characteristics across groups. For analytic purposes, all identified major mood disorders (MDD, bipolar disorder type 2, and dysthymia) were collapsed into a single category of depressive disorders, as were all identified anxiety disorders. Further ANCOVA models included severity of autistic behavior and degree of adaptive functioning in the FXS-affected child, characterized by scores obtained on the Autism Screening Questionnaire [ASQ; Berument et al., 1999] and the Vineland Adaptive Behavior Scales-2nd Edition [VABS-II; Sparrow et al., 1984], as covariates. In those cases of women with more than one FXS-affected child in the household, the child with the highest score on the ASQ and lowest score on the VABS was used in covariate analysis. FMR1 premutation length was observed to have a non-parametric distribution (Kolmogorov–Smirnov $Z = 1.379$, $P = 0.045$), therefore log-transformed data were used. All tests were conducted at the $P = 0.05$ (two-tailed) significance level.

RESULTS

Demographic and clinical characteristics of the study sample according to menopausal status are summarized in Table I. Nearly half (48%) of the women in the sample ($n = 22$) were postmenopausal at the time of interview, as defined by the absence of menses for the past year, while an additional 15% ($n = 7$) of women reported increasing menstrual irregularity and periodic hot flashes (i.e., grouped as peri-menopausal). Twenty-four women (37%) reported regular menstrual cycles and no symptoms of reproductive dysfunction. Compared to the average age of menopause 51 years of age [Kato et al., 1998; Schildkraut et al., 2001], post-menopausal women in the sample had a significantly lower average age of menopause (mean = 45.6 years, $SD = 4.3$; one-sample $t(21) = 5.890$, $P < 0.001$). Age at menopause appeared to be normally distributed, as demonstrated by a one-sample Kolmogorov–Smirnov test ($Z = 0.780$, $P = ns$). All of the postmenopausal women were naturally postmenopausal, with the exception of one case who was surgically menopausal (hysterectomy at age 38). Six (27%) were current users of hormone therapy (including the one who was surgically menopausal). Within the group of naturally menopausal women, 87% (20 of 23) experienced menopause prior to the national average age of 51, while the

remainder had ages of menopause at 51 ($n = 2$) and 53 ($n = 1$). Premutation length did not differ significantly between women who were postmenopausal and those who were not, even when adjusting for age ($F(2,43) = 2.798$, $P = 0.102$). Premutation length was not associated with age at menopause within the group of postmenopausal women ($r(22) = 0.151$, ns).

The majority of women in the study (74%; $n = 34$) reported a lifetime history of depressive and/or anxiety disorder, with 43% ($n = 20$) of the overall sample reporting a comorbid history. Other than mood and anxiety disorders, no other psychiatric disorders were detected. The types of identified depressive disorder cases (59% of overall sample, $n = 27$) were MDD (43% of overall sample, $n = 20$), dysthymia (4.3% of overall sample, $n = 2$), and bipolar disorder type 2 (11% of overall sample, $n = 5$). Of the women with a history of MDD or bipolar disorder (54% of overall sample, $n = 25$), 92% ($n = 23$) reported recurrent major depressive episodes (e.g., two or more episodes). A history of anxiety disorder(s) was found in 59% ($n = 27$) of all women in the sample, and two or more anxiety disorders were found among 41% of women ($n = 19$). Identified anxiety disorders included generalized anxiety disorder (9% of overall sample, $n = 4$), panic disorder with Agoraphobia (4% of overall sample, $n = 2$), panic disorder without Agoraphobia (24% of overall sample, $n = 11$), obsessive-compulsive disorder (9% of overall sample, $n = 4$), post-traumatic stress disorder (17% of overall sample, $n = 8$), and specific phobias (20% of overall sample, $n = 9$). A history of eating disorder (1 Anorexia Nervosa, 1 Binge Eating Disorder) was also present within the subset of women with a history of anxiety disorder.

The presence of a psychiatric history of depressive or anxiety disorder was associated with significantly longer premutation length, even after adjusting for age ($F(1,43) = 4.946$, $P = 0.031$; Fig. 1). An overall ANOVA model with each group of psychiatric disorders showed trend level significance for premutation length ($F(3,42) = 2.530$, $P = 0.070$). Women with comorbid depressive and anxiety disorder history were observed to have the highest number of CGG repeats (mean (SD) = 95.8 (16.9) compared to women free of psychiatric history (mean (SD) = 79.9 (7.4); $t(30) = 3.063$, $P = 0.005$). Premutation length among women with exclusive history of depressive disorders ($n = 7$, 15%), or anxiety disorders ($n = 7$, 15%), did not differ significantly from each other ($t(12) = 0.720$, $P = \text{ns}$). These findings did not appear to be differentially related to postmenopausal status, as postmenopausal, perimenopausal, and normal menstruating women did not differ with respect to history of depressive or anxiety disorders. Similarly, psychiatric history of depressive or anxiety disorders was not differentially associated with age at menopause ($t(20) = 0.372$, ns) or use of hormone therapy among postmenopausal women (Pearson $\chi^2(1) = 0.873$, ns). Among menopausal women, the age at menopause did not differ between those with and without a psychiatric history (45.4 ± 4.8 vs. 46.1 ± 3.2 , $P = \text{ns}$).

ANCOVA models covarying for both ASQ and VABS-II scores to control for severity of autistic and adaptive behavior in the FXS-affected offspring showed continued significant association between psychiatric history and premutation length ($F(1,42) = 5.042$, $P = 0.030$), with no significance for either ASQ or VABS-II score ($F(1,42) = 0.011$, $P = \text{ns}$, and $F(1,42) = 0.014$, $P = \text{ns}$, respectively). Further analysis controlling for marital status also showed continued significance for psychiatric history and premutation length ($F(1,40) = 4.325$, $P = 0.044$). Marital status itself was not associated with psychiatric history (Chi-

square = 3.723, $P = \text{ns}$), nor with age at menopause ($t(20) = 1.070$, $P = \text{ns}$). Approximately half of all women with history of a depressive disorder (14 of 27) reported onset prior to the birth of a FXS-affected child, and the distribution did not appear to differ between normal cycling, perimenopausal, and menopausal women (chi-square = 1.116, $P = \text{ns}$). Among menopausal women, age at menopause did not differ between those with depressive disorder onset prior to or after the birth of a FXS-affected child (45.0 ± 4.7 vs. 46.6 ± 5.7 , $t(10) = 0.504$, $P = \text{ns}$).

DISCUSSION

We identified a high rate of psychiatric dysfunction characterized by diagnostic clinical interviews in the present sample of women with FMR1 premutation. Further, there was a notably high rate of comorbid depressive and anxiety disorders, and a strong tendency for longer premutation lengths in women with psychiatric history as a whole. These data extend the field of available literature on psychiatric dysfunction in women with FMR1 premutation-carrying mothers of children with FXS, which to date has largely utilized self-report measures [Johnston et al., 2001; Hessler et al., 2005; Hunter et al., 2010; Lachiewicz et al., 2010], with a few notable exceptions of studies using clinical interviews [Roberts et al., 2009; Bourgeois et al., 2011; Reiss et al., 1993; Franke et al., 1998]. These data further previous work suggesting greater psychiatric disturbance with increasing premutation length [Johnston et al., 2001; Hunter et al., 2008], although not all studies have found such a relationship [Thompson et al., 1994; Franke et al., 1998; Hessler et al., 2005].

The results also revealed a significantly earlier age of menopause (mean = 45.6 years) compared to the general population average 51 years; [Kato et al., 1998; Schildkraut et al., 2001]. Further, the majority (87%) of menopausal women experienced menopause prior to the age of 51. However, in contrast to our hypothesis, neither presence of menopause nor age at menopause was found to be significantly associated with psychiatric history. For example, among menopausal women in the sample, those with and without psychiatric history showed no differences with respect to age at menopause (45.4 ± 4.8 vs. 46.1 ± 3.2 , $P = \text{ns}$). Exploratory analysis that removed the outlier who had surgical menopause due to hysterectomy at age 38 (and who had a history of both MDD and panic disorder, and a premutation length of 84), did not appear to alter the results with respect to age at menopause in those with and without psychiatric history (mean (SD) 46.0 (4.3) vs. 46.1 (3.2)), nor with respect to greater premutation length among those with psychiatric history ($F(1,42) = 4.963$, $P = 0.031$). The lack of a significant association between psychiatric and reproductive system dysfunction may have been confounded by the high rate of psychiatric dysfunction in the sample overall and/or may have been a cohort effect. While there was overlap in the range of repeat length among women with no psychiatric history ($n = 12$) relative to those with depressive or anxiety disorder history ($n = 36$), the finding of significantly longer repeat length among women with psychiatric history remained significant after controlling for age and other variables. The collective evidence supports further investigation in to the clinical significance of increasing premutation length on risk of psychiatric disorders. Our data add to previous work by Hunter et al. [2010] in their study of self-reported psychiatric history and reproductive system function in women with the

FMR1 premutation, in which greater risk of depression was evident in women with symptoms of ovarian dysfunction.

Our results also included an approximate 11% rate ($n = 5$) of bipolar disorder type 2 in the sample. While this is a higher rate than previously reported in the available literature to date, it should be noted that emphasis on self-report measures in most studies to date on psychiatric dysfunction in the *FMR1* premutation population may have failed to fully identify cases of bipolar disorder separate from depression. Previous studies in the general population have demonstrated a high rate of misdiagnosis of bipolar disorder type 2 as MDD [Smith et al., 2011].

The neuroendocrinological overlap between mood and anxiety disorders and reproductive system dysfunction in women suggest an underlying pathophysiological mechanism in the increased risk for psychiatric and reproductive system dysfunction in women with FMR1 premutation that is not yet fully understood. Women, in general and on average, suffer from depression at approximately double the rate of men [Eaton et al., 2007], and mood and anxiety disorders are further compounded during the time of perimenopause and menopause [for review, see Soares and Maki, 2010]. Women, compared to men, who carry the FMR1 premutation may be at particularly vulnerable risk for mood disorders given inherent, FMR1-premutation specific neuroendocrine alterations in both ovarian function and mood regulation. Indeed, other data suggest that the complex neuronal effects of the FMR1 premutation on mood and anxiety regulation is moderated by sex, wherein women are more affected [Hunter et al., 2010]. Data in that study also showed that women with indication of ovarian insufficiency (i.e., irregular cycles) reported higher rates of depression and anxiety. Longitudinal data assessing psychiatric function over time as premutation carriers age and enter menopause are needed to advance understanding of mechanistic links between the psychiatric and reproductive system dysfunction in this population.

During menopause, women in general face increased risk for mood and anxiety disorders, likely due to significant fluctuations of estrogen and other hormones [Soares and Maki, 2010]. Women experiencing FMR1-associated early menopause or POI may experience similar deleterious hormonal fluctuations that may further increase risk for mood and anxiety disorders. Hypothalamic–pituitary-axis system function may play a role in the psychiatric functioning of women the FMR1 premutation, as suggested by a recent study showing links between stressful life events, the cortisol awakening response, and mid-range CGG repeats [Seltzer et al., 2012]. Further recent data suggests polymorphisms of the *CRHR1* gene, which associate with differences in HPA axis function, interact with individual response stress to predict the severity of anxiety and depressive symptoms in women with the FMR1 premutation [Hunter et al., 2012]. Sex differences in FMR1 premutation-associated medical and psychological phenomena remains to be methodically explored, and the potential moderating effects of menopause-related variables in the relationship between premutation length and psychiatric history remain to be determined. Small sample size and the cross-sectional nature of the present study were inadequate to test for the existence of such interactions.

The specific hormonal milieu and reproductive profile associated with FMR1 premutation has yet to be fully characterized. Data from controlled studies on women with the FMR1 premutation suggest that, despite regular menstrual cycles, women with the premutation experience early ovarian aging that may result from decreased follicle number and function, as reflected by lower inhibin B, inhibin A, and P4 levels [Rohr et al., 2008]. The elevated FSH often observed in FMR1 premutation carriers with symptoms of POI is accompanied by diminished anti-Müllerian hormone (AMH), which may be a useful clinical biomarker of ovarian function in women with FMR1 premutation [Rohr et al., 2008]. Ongoing NIH investigations, notably efforts to create a patient registry of natural history of reproductive and overall health, including psychiatric disorders, in girls and women with the premutation, hold the promise to advance collective understanding of potential interlinking phenomena as participants are followed over time to assess the possible effects of this genetic abnormality.

Limitations of the present study include potential participation bias, given that the invitation letter indicated that we would be investigating reproductive health and mood. Also, the clinicians who administered the SCID to participants were aware that each had the FMR1 premutation. Further, the genetic data was drawn from a small sample and included only a small number of women with high-end CGG repeats. In addition, women with the FMR1 premutation who have one or more children with FXS may also be at risk for anxiety and/or depression because of the stress associated with the care of a child with developmental disabilities [Wheeler et al., 2007]. We did not obtain comparable data from a control group of women without the FMR1 premutation, and future prospective studies on both psychiatric and reproductive dysfunction in female FMR1 premutation carriers might include nulliparous women and parous women without FXS-affected offspring. A future study that considers reproductive system functioning in a group of control group of FMR1 premutation carriers without an FXS-affected child, as well as a group of women without the premutation with children matched for degree of intellectual disability, would allow for further improved understanding of potential underlying mechanisms. Such investigations appear strongly warranted to expand our collective understanding of distinctive FMR1 premutation phenotypic problems and disorders.

Despite the aforementioned limitations, this study is noteworthy for its use of clinician-administered assessments of DSM-IV diagnostic psychiatric history. Only one previous study of FMR1 premutation carriers has conducted clinical interviews, and that study focused upon FXTAS in both men and women [Bourgeois et al., 2011]. The clinical interview employed in this study allowed for the detailed characterization of psychiatric dysfunction in this population. Indeed, two-thirds of women with a history of depressive disorders were found to have recurrent depressive episodes, suggesting a recurrent mental illness. The observed rates of depressive and anxiety disorders, and their comorbidity, are higher than rates in general U.S. population studies, such as the recent Study of Women's Health across the Nation (SWAN) Mental Health Study [Cyranowski et al., 2012]. Further prospective evaluation of depression and the biomarkers of depression in women with FMR1 premutations hold the promise to identify the underlying depression-related pathophysiology that may further perturb reproductive dysfunction. This is supported by recent data from the Harvard Study of Mood and Cycles, which found that women with depression history

(treated or not) have an earlier age at menopause than women without history of depression [Cohen et al., 2006].

In summary, our results provide evidence of elevated psychiatric morbidity and comorbidity, and an earlier age of menopause in a sample of women with FMR1 premutation. Further, the data also suggest that premutation length may be related to psychiatric functioning. Future investigations may benefit from inclusion of biochemical reproductive markers in addition to psychiatric history, as the association between these two domains of FMR1 premutation-associated medical and psychological phenomena, and their sex-specific natures, remains to be determined.

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FIG. 1.

Premutation lengths among women with no psychiatric history ($n = 12$) compared to those with histories of anxiety disorders alone ($n = 7$), depressive disorders alone ($n = 7$), or comorbid anxiety and depressive disorders ($n = 20$). Menopausal group status is noted for all subjects.

TABLE I

Sample Characteristics

	Not menopausal (n = 17)	Peri-menopausal (n = 7)	Menopausal (n = 22)
	Mean (SD)		
Age	46.2 (6.2)	43.7 (5.7)	50.1 (4.1)
Premutation length (number of repeats)	97.2 (22.3)	89.0 (21.7)	85.5 (15.0)
WAIS-III score	108.5 (18.1)	100.3 (9.1)	103.8 (12.5)
Age at menopause (years)	—	—	45.6 (4.3)
Total number of offspring	2.9 (0.9)	2.6 (0.8)	2.9 (0.9)
Number of FXS-affected offspring	1.5 (0.7)	1.6 (0.5)	1.3 (0.5)
ASQ	11.0 (9.3)	12.7 (6.0)	9.7 (9.8)
VABS-II	48.5 (18.9)	47.7 (13.0)	40.4 (24.9)
Marital status	n per group		
Single	0	1	0
Married	11	5	12
Divorced	5	1	10
Widowed	1	0	0