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Clinically Significant Psychiatric Symptoms among Male Carriers of the Fragile X Premutation, with and without FXTAS, and the Mediating Influence of Executive Functioning

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Abstract

Objectives—To clarify the neuropsychiatric phenotype of fragile X-associated tremor/ataxia syndrome (FXTAS), and assess the extent to which it is mediated by the dysexecutive syndrome that is a major feature of the disorder.

Methods—We examined the prevalence of clinically meaningful psychiatric symptoms among male carriers of the fragile X premutation, with and without FXTAS, in comparison with men with a normal allele. Measures included the Neuropsychiatric Inventory (NPI), Symptom Checklist-90-R (SCL-90-R), and the Behavioral Dyscontrol Scale (BDS), a measure of executive functioning. Between-group differences were evaluated using logistic regression, followed by a mediation analysis with ordinary least squares regression to assess the contribution of dysexecutive syndrome to the observed psychiatric domains.

Results—Men with FXTAS showed higher rates of clinically significant symptoms overall and in specific domains: somatization, obsessive-compulsive, depression, anxiety, psychoticism, agitation/aggression, apathy/indifference, irritability, and nighttime behavior problems. *Post hoc* analyses suggested that findings of psychoticism among men with FXTAS may be associated with participants' accurate acknowledgement of cognitive and physical dysfunction, rather than reflecting psychosis. Asymptomatic carriers showed no evidence of clinically significant

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psychiatric symptoms, but when all carriers were compared with men having a normal *FMR1* allele, executive function deficits were found to mediate scores in several domains on both NPI and SCL-90-R.

Conclusions—Building on prior research, the results provide evidence that the psychiatric phenotype for men includes clinically meaningful depression, hostility, and irritability, in association with behavioral and attentional disinhibition. It is likely that these problems reflect the effects of impaired executive functioning.

Keywords

fragile X; premutation; fragile X tremor/ataxia syndrome; FXTAS; psychiatric symptoms; executive functioning

Introduction

Fragile X-associated tremor/ataxia syndrome (FXTAS) is a late-onset neurodegenerative disorder associated with a trinucleotide (CGG) repeat expansion in the fragile X mental retardation 1 (*FMR1*) gene (Hagerman, Leehey, Heinrichs, et al. 2001; Jacquemont, Hagerman, Leehey, et al. 2003). Normal *FMR1* alleles have six to 44 CGG repeats. Individuals with ≥200 repeats have the *full mutation,* which results in fragile X syndrome, the most common genetic cause of intellectual disability. People with 55 to 200 repeats have the fragile X *premutation.* They may experience mild neurodevelopmental anomalies, including cognitive deficits and anxiety disorders.(Sherman, Marsteller, Abramowitz, et al. 2002; Cornish, Kogan, Turk, et al. 2005; Loesch, Hay, Mulley, et al. 1994; Loesch, Bui, Grigsby, et al. 2003; Moore, Daly, Schmitz, et al. 2004; Moore, Daly, Tassone, et al. 2004; Loesch, Churchyard, Brotchie, et al. 2005).

A large percentage (approximately 40%) of male carriers of the *FMR1* premutation develop FXTAS. Gait ataxia and action tremor are the defining features of FXTAS, but affected individuals also may experience peripheral neuropathy, parkinsonism, autonomic disorders, and deficits in executive cognitive functioning, working memory, and information processing speed (Hagerman et al. 2001; Jacquemont et al. 2003; Bacalman, Farzin, Bourgeois, et al. 2006; Grigsby, Brega, Jacquemont, et al. 2006; Brega, Goodrich, Bennett, et al. 2008; Grigsby, Brega, Engle, et al. 2008; Grigsby, Leehey, Jacquemont, et al. 2006; Grigsby, Brega, Leehey, et al. 2007; Leehey, Munhoz, Lang, et al. 2003). Incidence and prevalence are age-related: whereas only 17% of male premutation carriers in their 50s have FXTAS, up to 75% of male carriers in their 80s have symptoms consistent with the syndrome (Jacquemont, Hagerman, Leehey, et al. 2004).

The psychiatric phenotype of male premutation carriers has been described, but is not fully understood. However, men with FXTAS appear to have more significant psychiatric symptoms than do carriers without the syndrome (Hagerman et al. 2001; Jacquemont, Farzin, Hall, et al. 2004; Bourgeois, Cogswell, Hessl, et a. 2007). Anxiety (Jacquemont et al. 2004), deficits in social cognition, and obsessive-compulsive symptoms (Cornish, Kogan, Turk, et al., 2005; Dorn, Mazzocco, Hagerman, 1994; Hessl, Tassone, Loesch, et al. 2005) have been reported among male carriers *without* FXTAS. Additionally, using the Symptom

Checklist-90-Revised (SCL-90-R) (Derogatis, 1994), Hessl et al. (2005) found that men with FXTAS scored higher than a normative sample on somatization, interpersonal sensitivity, depression, anxiety, phobic anxiety, and psychoticism. Subsequent research (Bacalman et al. 2006) showed a higher prevalence of symptoms of depression, apathy, agitation/aggression, disinhibition, and irritability among men with FXTAS than among control participants. Seritan, Nguyen, Farias, et al. (2008) reported high rates of depression and anxiety among men with FXTAS-related dementia, and Bourgeois, Seritan, Casillas, et al. (2011) found lifetime prevalence of mood and anxiety disorders of 65% and 52%, respectively. Seritan, Bourgeois, Schneider, et al. (2013) found that the age of onset for such disorders is older among male carriers than among the general population, but occurs before the appearance of neurologic signs of FXTAS, suggesting the possibility that mood and anxiety disorders represent an early symptom of FXTAS.

Although earlier investigators have examined psychiatric functioning among male premutation carriers, existing studies often have been limited by small sample sizes and/or a focus on the presence of symptoms of any level of severity. There is still limited information available regarding the extent to which symptoms within specific psychiatric domains are severe enough so as to be clinically significant. Moreover, it is unclear whether the psychiatric disorders apparently identified in FXTAS represent conventional psychiatric diagnostic categories, or are related to the dysexecutive syndrome that has been shown to be a major feature of the behavioral-emotional phenotype (Brega et al., 2008; Grigsby et al., 2008).

Therefore, the objectives of this study were to: 1) determine whether male premutation carriers with and without FXTAS exhibit greater frequency of clinically significant psychiatric symptoms than do healthy controls, and 2) assess whether psychiatric symptoms can be explained by deficits in executive functioning. To those ends, we administered two informant-report measures of psychiatric symptoms to determine the presence of clinically meaningful symptoms within and across psychiatric domains among male premutation carriers, comparing those with and without FXTAS to healthy controls. We also administered a measure of executive functioning (EF), and examined whether limitations in EF mediate the presence of psychiatric symptoms.

Methods

The study protocol was approved by the institutional review boards of the University of Colorado Denver and the University of California, Davis. Participants provided informed consent after study procedures were fully explained.

Participants

Sample Description—Participants were 112 English-speaking men age 41 to 89, 98.2% of whom were White. Participants were categorized into three groups: 1) premutation carriers (PMCs) meeting diagnostic criteria for definite or probable FXTAS (Jacquemont et al., 2003) (n=43); 2) asymptomatic premutation carriers (APCs, n=32); and 3) control participants with normal *FMR1* alleles (n=37).

Recruitment—Study enrollment was described in an earlier report (Grigsby et al. 2008), but is summarized here. PMCs were identified through involvement in pedigree studies conducted at the participating institutions, through participation in the National Fragile X Foundation or fragile X-related support groups, and through the clinical practices of study co-investigators. Control participants were recruited from families of PMCs or through advertisements. Exclusion criteria included the following: sensory/language deficit or medical condition making participation impossible (e.g., severe deconditioning); medical condition or treatment with the potential to adversely affect cognitive or emotional functioning (e.g., concurrent corticosteroids or opiates); head injury involving more than momentary loss of consciousness; medically intractable or surgically treated epilepsy; definitively diagnosed movement disorders other than FXTAS; stroke; history of schizophrenia, manic episodes, or psychotic depression; history of toxic encephalopathy, encephalitis, or bacterial meningitis; and delirium associated with an acute medical condition. In addition, because information about each participant's functional status was obtained from the participant as well as a family member or friend, only men with an available informant who was knowledgeable about the potential participant's functional status were enrolled in the study. As female PMCs were not thought to develop FXTAS at the time this study was designed and proposed, women were not enrolled.

Procedures

Participants underwent neurological evaluation, brain MRI, and genetic testing, which allowed for categorization of participants into the three study groups. Neuropsychological tests also were administered, as were two instruments capturing the presence and severity of psychiatric symptoms: the Revised Symptom Checklist-90 (SCL-90-R) (Derogatis, 1994) and the Neuropsychiatric Inventory (NPI) (Cummings, Mega, Gray, 1994). Formal diagnostic psychiatric interviews were not conducted. The primary neuropsychological instrument used in this study was the Behavioral Dyscontrol Scale (BDS; Grigsby, Kaye, Robbins, 1992), a measure of the capacity for autonomous regulation of motor behavior and attention, on which people with FXTAS show clinically significant, progressive impairment (Grigsby, Brega, Engle, et al., 2008)

Symptom Checklist-90-Revised (SCL-90-R)—This measure (Derogatis, 1994) contains 90 items assessing the degree to which an individual has been distressed by specific psychiatric symptoms during the previous seven days. Items are answered on a 5-point scale, ranging from 0 (not at all distressed) to 4 (extremely distressed). From these items, scores for nine psychiatric dimensions are computed: somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoia, and psychoticism. Three measures of overall functioning also are computed. The Global Severity Index represents the average score across items, providing a summary measure of psychiatric functioning. The Positive Symptom Distress Index reflects the average score for symptoms present, providing a measure of overall symptom severity. The Positive Symptom Total indicates the number of symptoms reported, and thus reflects breadth of disorder.

Raw scores for each dimension and index were converted to T-scores (mean = 50, standard deviation = 10) using normative data for male community residents without psychiatric

disorder (Cummings et al. 1994). Higher values represent more severe symptoms. Using criteria suggested by Derogatis (1994) and implemented in prior studies (Butterbaugh, Rose, Thomson, 2005), T-scores ≥63 for each dimension and index score were interpreted as representing indicate clinically significant symptomatology. In addition to the index scores, we examined two additional measures of overall psychiatric symptomatology (or "caseness"). First, we computed the number of dimensions for which a participant scored in the clinical range. Second, using criteria developed by earlier investigators, participants with Global Severity Index T-scores ≥63, or with two or more dimension scores ≥63, were identified as "cases" having a high likelihood of meeting diagnostic criteria for psychiatric disorder.

Although SCL-90-R data are typically obtained by self-report, we analyzed data collected from knowledgeable informants (i.e., caregivers), 95% of whom were spouses/significant others or adult children of study participants. Each informant indicated the degree to which the study participant had been distressed by specific symptoms during the previous seven days. Using informant-report data allowed us to compare performance on the SCL-90-R to data collected using the NPI, which is designed as an informant interview. In addition, use of informant-reports eliminated the possibility that the impaired insight frequently associated with FXTAS would affect the validity of data for men with FXTAS (Brega et al. 2008; Grigsby et al. 2008).

Neuropsychiatric Inventory (NPI)—The NPI is a widely used measure of non-cognitive psychiatric symptoms among individuals with dementia (Cummings et al. 1994). Designed as an informant interview, the NPI assesses the presence, frequency, and severity of observable behavioral symptoms within 12 neuropsychiatric domains: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability, aberrant motor behavior, nighttime behaviors, and appetite/eating behaviors. For each domain in which symptoms occurred during the past month, the frequency (1 = occasionally, 2 = often, 3 = frequently, 4 = very frequently) and severity of symptoms (1 = mild, 2 = moderate, 3 = marked) is rated. The total score within a domain equals the product of the frequency and severity ratings. The total NPI score reflects the sum of the 12 domain scores. We examined group differences in domain and total scores indicative of clinically significant symptomatology. Using criteria applied in earlier research (Schneider, Tariot, Lyketsos, 2001), we identified domain scores of 4 or greater as being in the clinical range.

Behavioral Dyscontrol Scale (BDS)—The BDS (Grigsby, Kaye, 1996) is a 9-item, 27-point measure adapted from the work of Luria (1980), assessing the capacity for behavioral self-regulation. Seven items involve performance of motor tasks with the hands, one involves working memory and attentional control, and the final item is a measure of the participant's ability to assess the accuracy of his or her own performance. The BDS has high internal consistency (Cronbach's alpha=0.87), interrater reliability (ICC for individual items and total score>0.9), and retest reliability (r=0.86 over 6 months and r=0.89 over 8 weeks) (Grigsby et al., 1992; Suchy, Blint, Osmon, 1997).

Mini-Mental State Exam (MMSE)—The MMSE (Folstein, Folstein, McHugh, 1975) is a mental status exam with a 30-point scale, designed as a valid and reliable measure to quickly classify the severity of cognitive impairment. Cognitive impairment is indicated by a score of 23 or less, while dementia is indicated by a score of < 20. A score of 10 or less indicates severe cognitive impairment. The MMSE, which was administered to all participants, was used in this study as a covariate in *post hoc* analyses.

Purdue Pegboard Test (PPT)—The PPT (Tiffin & Asher, 1948) is a test of motor function in which subjects rapidly insert small metal pegs into holes on a pegboard, first using the right hand, then the left, and finally both hands simultaneously. The number of pegs inserted during the 30-second trial using the dominant hand was used as a covariate in *post hoc* analyses.

Data Analysis

Data were analyzed using both SAS and SPSS, including the Process macro for SPSS (v 2.15), written by Hayes to facilitate the analysis of moderating and mediating variables (Hayes, 2013). Group differences in the prevalence of clinically significant psychiatric symptoms were examined using logistic regression. Separate analyses were conducted to compare control participants to: 1) men with FXTAS and 2) APCs. The false discovery rate was used to control for inflation in the rate of Type 1 error. Following these between-groups analyses we used ordinary least squares regression using the Process macro to evaluate the influence of executive functioning as a factor mediating NPI and SCL-90-R raw domain scores, comparing all PMCs with controls.

Results

Preliminary Analyses

Table 1 presents demographic information about the sample. The average age in each of the three groups was between 60 and 68 years old. Participants in the three groups had a mean of 15.4 to 16.7 years of education. The vast majority of study participants were non-Hispanic White, reflecting the demographic composition of the population from which we were able to recruit a sample. Whereas APCs did not differ from the control group in age, education, race, or ethnicity, men with FXTAS were significantly older on average and had marginally lower levels of education than did participants in the control group. The mean ages of the two groups of carriers differed significantly ($t = -4.56$, $p < 0.001$), although they did not differ in education or race and ethnicity. This is likely a reflection of the fact that age is associated with the development and progression of FXTAS in later life among PMCs.

SCL-90-R: Presence of psychiatric symptoms

Overall psychiatric functioning was impaired among men with FXTAS (Table 2). More than 44% had SCL-90-R Global Severity Index scores in the clinical range, a significantly greater prevalence than seen among controls. Clinically meaningful scores on the Positive Symptom Distress Index and Positive Symptom Total Index also were significantly more common among participants with FXTAS than controls. Further, more than half of men with FXTAS met criteria for “caseness,” a significantly larger prevalence than seen among controls.

Table 2 shows the prevalence of clinically significant psychiatric symptoms by group. Compared to controls, men with FXTAS had significantly higher rates of clinically meaningful symptoms for five dimensions: somatization, obsessive-compulsive, depression, anxiety, and psychoticism. Whereas 5.7% to 17.1% of controls had T-scores ≥63 for these dimensions, approximately one-third to one-half of participants with FXTAS had scores of this magnitude. Participants with FXTAS also had a marginally higher rate of symptoms for the phobic anxiety dimension ($p < 0.06$). Although more than one-quarter of men with FXTAS experienced serious symptoms of interpersonal sensitivity and hostility—a rate approximately two times that seen among controls—these differences did not reach statistical significance.

Asymptomatic carriers showed no evidence of clinically significant psychiatric symptoms (Table 2). For each dimension and overall score, the prevalence of clinically meaningful symptoms among these participants was similar to that of controls.

Neuropsychiatric Inventory (NPI)—Table 3 presents the prevalence of clinically significant psychiatric symptoms by NPI domain (i.e., domain score ≥4). Compared to controls, participants with FXTAS were more likely to experience meaningful psychiatric symptoms in five domains (agitation/aggression, anxiety, apathy/indifference, irritability, and nighttime behavior problems), and were marginally more likely to experience clinically meaningful symptoms of depression/dysphoria. Between 23.1% and 39.5% of participants affected by FXTAS experienced clinically meaningful symptoms in these domains, compared with 3.1% to 9.4% of controls. Although the prevalence of clinically significant symptoms of disinhibition, aberrant motor behavior, and appetite/eating changes was substantially larger among FXTAS than control participants, these differences were not statistically significant.

Additionally, men with FXTAS had a significantly greater burden of non-cognitive psychiatric symptoms than controls (Table 3). Whereas 79.5% of premutation carriers with FXTAS had total NPI scores indicating clinically significant non-cognitive psychiatric symptoms (≥4), only 15.6% of controls had scores of similar magnitude.

Consistent with the SCL-90-R analyses, NPI data suggested no significant impairment in the functioning of APCs. Compared to controls, these participants showed no clinically significant psychopathology in any NPI domain or on the overall NPI score (Table 3).

Discrepancies between SCL-90-R and NPI—Results of analyses based on the SCL-90-R and the NPI highlighted a seeming discrepancy with regard to psychotic symptomatology. Using the SCL-90-R, men with FXTAS were found to experience clinically meaningful symptoms of psychoticism at a significantly higher rate that controls. Importantly, however, the NPI domains capturing delusions and hallucinations—two key diagnostic criteria for psychosis—showed no significant differences between men with FXTAS and controls. This suggested a difference in the way psychosis is conceptualized by the two instruments.

To clarify the discrepancy between these results, *post hoc* analyses were conducted to identify the components of the SCL-90-R psychoticism dimension on which men with FXTAS experience significant symptoms. Using multiple regression, we examined the relationship between the group variable (FXTAS versus control) and the individual data elements included in the SCL-90-R psychoticism dimension. Men with FXTAS differed significantly from controls on only two items: 1) Item 87, *the idea that patients thought something serious was wrong with their body* ($t = 2.40$, $p < 0.05$), and 2) Item 90, *the idea that patients thought something was wrong with their mind* ($t = 2.20$, $p < 0.05$).

In the context of a neurodegenerative condition marked by tremor, ataxia, cognitive impairment, and other clinical problems, it is reasonable that men with FXTAS might believe that something is wrong with their bodies and/or minds. To examine the degree to which FXTAS symptoms account for group differences on these items, we repeated the regression analyses reported above, including key characteristics of FXTAS as covariates. When examining group differences in the perception that something is wrong with one's body (Item 87), we included participants' dominant-hand score on the Purdue Pegboard Test (PPT), which we used as a proxy for severity of action tremor. Inclusion of PPT score eliminated the group difference between FXTAS and control participants on item 87. For the item concerning patients' belief that something is wrong with their mind (Item 90), we controlled for performance on the Mini-Mental State Exam (MMSE) and the Behavioral Dyscontrol Scale (BDS), a measure of executive functioning (Grigsby, Kaye, Robbins, 1992). After controlling for these measures, group differences on Item 90 became nonsignificant.

Mediation Analysis

To assess the influence of executive functioning on clinical domains in the NPI and SCL, we used multiple regression with Hayes's Process macro for SPSS, which is based on a bootstrapping approach. Dependent variables were the total raw score for each domain on the SCL, and for the Frequency and Severity ratings of each domain of the NPI. Because of a lack of variability, the Euphoria/Elation domain was not analyzed. Regression models controlled for age and education as covariates, with group membership (all premutation carriers vs. controls) as independent variable, and total score on the BDS as the mediating variable. Table 4 presents the effect and 95% confidence interval of these analyses.

On the NPI, those domains for which the indirect effect of executive functioning was significant included frequency and severity of delusions, hallucinations, depression, apathy/indifference, irritability, and the frequency of abnormal nighttime behaviors, and severity of disinhibition. On the SCL-90-R, a significant mediating effect was observed for obsessive-compulsive behavior, depression, hostility, psychoticism, and positive symptom distress.

Discussion

The current study expands our understanding of the neuropsychiatric phenotype of male carriers of the fragile X premutation. Although earlier studies explored psychiatric symptoms among male carriers (Bacalman et al. 2006; Bourgeois et al. 2007; Hessl et al.

2005), the prevalence of clinically significant psychiatric disturbance in this group has been inadequately addressed. The present study sought to extend prior research by examining the frequency of clinically significant psychiatric symptoms among PMCs with and without FXTAS. In addition, we were interested in whether any of these symptom domains were mediated by deficits in executive functioning. The primary findings are that: 1) compared with healthy controls, male premutation carriers with FXTAS, but not those without FXTAS, exhibit a higher rate of clinically significant psychiatric symptoms; 2) the meaning of ostensibly psychotic symptoms is not consistent across the SCL-90-R and NPI; and 3) rather than reflecting conventional psychiatric disorders, a number of specific psychiatric symptoms appear to be a function of deficits in executive functioning.

Greater prevalence of clinically significant symptomatology—Men with FXTAS experience clinically important psychiatric symptoms at a significantly higher rate than do men with a normal *FMR1* allele. Previous research found that men with FXTAS had significantly higher T-scores than a normative sample for six SCL-90-R dimensions: somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, phobic anxiety, and psychoticism (Hessl et al. 2005). In this study, more than 44% of men with FXTAS had T-scores for the SCL-90-R Global Severity Index suggesting psychiatric disturbance, and 53% met criteria for caseness. Psychopathology was clinically significant for the same domains, with the exceptions of interpersonal sensitivity and phobic anxiety, the difference for the former falling just short of significance ($p < 0.06$), despite a seemingly large difference between groups.

On the NPI (Schneider et al. 2001), nearly 80% of men with FXTAS were characterized as experiencing symptoms within the clinical range. On the NPI, men with FXTAS were more likely than controls to experience clinically significant symptoms in five domains (agitation/aggression, anxiety, apathy/indifference, irritability, and nighttime behavior problems), but (in contrast to the SCL-90-R) were only marginally more likely ($p < 0.10$) to experience clinically meaningful depression/dysphoria. These results are generally consistent with those of Bacalman et al. (2006), who found that men with FXTAS were more likely than control participants to experience *any* symptoms of agitation/aggression, depression/dysphoria, apathy/indifference, disinhibition, and irritability. The current results, however, indicate that symptoms in these domains are not merely more prevalent, but are more likely to be clinically important.

Findings for asymptomatic carriers—Importantly, our results suggest that male premutation carriers without FXTAS are not more likely than controls to experience clinically significant psychiatric symptoms. This finding is in contrast to earlier evidence of elevated rates of psychiatric symptoms in this group (Hessl et al. 2005). Although asymptomatic carriers may be more likely to experience psychiatric symptoms, or even a higher severity of symptoms within the domains addressed by the SCL-90-R and NPI, our results suggest that these are generally not *clinically meaningful*. It is possible that earlier findings of psychiatric disturbance among asymptomatic carriers may reflect preclinical symptoms among a subset of participants who do not currently have a movement disorder, but may develop FXTAS eventually. Subtle executive cognitive and psychiatric signs and

symptoms of FXTAS could precede tremor and ataxia, and not be recognized as signaling the onset of the disorder. This discrepancy in findings also may reflect the different methodological approaches used to evaluate psychiatric symptomatology in the different studies.

Consistency and discrepancies in NPI and SCL-90-R results

Unlike earlier work, this study examined the prevalence of psychiatric symptoms using both the SCL-90-R and the NPI. Although these instruments do not examine precisely the same domains of functioning, each addresses symptoms of anxiety, depression, and psychotic behavior. Comparing results across the two instruments provides a clearer picture of psychiatric disturbance in FXTAS. Moreover, the relative redundancy in the SCL-90-R and NPI findings may be reason for confidence in our results.

The most consistent finding across SCL-90-R and NPI is for anxiety, which appears to be a significant problem for men with FXTAS. The prevalence of anxiety was similar across instruments, with between one-quarter and one-third of men with FXTAS experiencing symptoms in the clinical range. The data provide a less consistent picture of depression in FXTAS. On the SCL, 48.8% of men with FXTAS were found to experience clinically meaningful depression, a rate significantly higher than among controls. In contrast, the NPI identified only 23.1% of participants with FXTAS as having clinically meaningful depression, marginally higher than observed among controls. As the NPI and SCL-90-R were administered to spouses/informants during the same interview, the discrepancy may suggest a difference in how the construct is measured by the instruments.

Although the NPI depression subscale showed only a marginal difference between FXTAS and control participants, men with FXTAS were significantly more likely than controls to experience clinically meaningful symptoms in the NPI apathy/indifference and nighttime behavior domains. Group differences in these domains, which address key symptoms of depression (e.g., reduced enthusiasm for usual interests, trouble sleeping), support the conclusion that men with FXTAS experience greater dysphoric affect than controls. These results reflect the presence of symptoms associated with, but not necessarily diagnostic of major depression. Given the relationship of apathy with problems in executive functioning, it is possible that apathy is more problematic than depression, and that items on the SCL-90-R do not make this distinction in the same way as the NPI. In fact, four items on the SCL-90-R appear on the face of it to have more in common with NPI apathy/indifference than with NPI depression (decreased libido, low energy, no interest in things, and experiencing life as requiring more effort).

Clarifying previous research (Hessl et al. 2005), our results suggest that psychoticism/psychosis *per se* is not a feature of FXTAS. Although men with FXTAS showed more clinically meaningful symptoms on the SCL-90-R psychoticism dimension when compared to controls, *post hoc* analyses suggest that this finding was a result of group differences on two specific SCL-90-R items, which address patients' belief that something is wrong with one's body or mind. Given that motor and cognitive impairment are hallmarks of FXTAS, it is reasonable that an individual with the disorder might perceive himself in this way. Indeed, when measures of motor functioning and cognitive status were controlled, these group

differences became nonsignificant. These results, and the fact that men with FXTAS are not more likely than controls to experience delusions or hallucinations—a finding of both this study and earlier work (Bacalman et al. 2006)—support the conclusion that psychosis of a schizophrenic type is not a symptom of FXTAS.

Comparison to other neurodegenerative conditions—Psychiatric symptoms are common in FXTAS, as is the case in other neurodegenerative disorders. In this study, one-quarter to one-half of participants with FXTAS experienced serious symptoms of depression. In comparison, depressive symptoms are present in up to 87% of individuals with Alzheimer's disease (AD) (Mendez & Cummings, 2003), with 25% experiencing major depression (Lyketsos & Lee, 2004). Depression also is a cardinal symptom in other movement disorders. Up to 50% of individuals with Parkinson disease (PD) experience depressive symptoms, whereas 10% meet criteria for major depressive disorder (Weintraub & Stern, 2005). Although depressed mood is common in the preclinical phase of dementing disorders (Berger, Fratiglioni, Forsell, 1999), asymptomatic carriers in the current study—some of whom may eventually convert to FXTAS—did not experience higher than expected rates of depression.

Significant symptoms of apathy also were common in the FXTAS sample. Nearly 40% of men with definite or probable FXTAS showed signs of significant apathy. Such symptoms occur at a high rate in other neurodegenerative disorders as well; for example, apathy has been reported in as many as 37% of patients with AD (Starkstein, Petracca, Chemerinski, 2001), and it is especially likely in those disorders involving a dysexecutive syndrome (e.g., fronto-temporal dementia [FTD]). Moreover, in this study, the NPI apathy and indifference domain was found to be mediated by impaired executive functioning.

Mediating influence of executive impairment—One hypothesis tested by this study was that certain features of the psychiatric phenotype of FXTAS, rather than reflecting more conventional psychiatric diagnoses, are mediated by impaired executive functioning. In particular, we were concerned with those behavioral disorders that characterize what Baddeley and Wilson (1988) called the *dysexecutive syndrome.* In particular, these include impulsivity, difficulty initiating purposeful behavior, failures in planning, and an inability to make and maintain an effort in goal-directed tasks. The mediation analyses provided considerable support for this hypothesis. Most noteworthy were contributions of the dysexecutive syndrome to depression, apathy, irritability, hostility, and severity of disinhibition. The BDS, which was developed as a measure of the capacity for behavioral and attentional self-regulation, contributed to all of these.

For several of these domains of psychopathology the relationship seems fairly straightforward. Disinhibition, irritability, and hostility, for example, may readily be associated with a deficient ability for self-control. The same is true for agitation and aggression, which also are common in FXTAS, as in other forms of dementia. In one study, for example, approximately 24% of patients with a diagnosis of dementia were reported to experience such symptoms (Lyketsos, Steinberg, Tschanz, 2000), a prevalence almost identical to that seen among participants with FXTAS in the current study (23.1%). This is consistent with our finding that executive deficits were a significant mediator of severity of

disinhibition on the NPI. The relationship is somewhat less clear with hallucinations and delusions on the NPI, although spouses endorsing a greater frequency of delusions may be explained in part by patients' questionable attributions about the actions of others, in association with limited ability to think critically about those attributions. Moreover, spouses themselves may interpret certain statements by their husbands incorrectly, not really understanding what they are trying to say. Overall, however, it seems likely that the observed psychopathology may be explained to a large extent by the presence of a dysexecutive syndrome, especially phenomena that are primarily behavioral in nature.

Limitations—The study is limited particularly insofar as the SCL-90-R and NPI were obtained from caregiver report. While the NPI was designed to be administered to caregivers and others who know the patient well, the SCL-90-R was intended primarily to be completed by self-report. Consequently, scores on this measure, including caseness, and the results pertaining to the SCL-90-R should be interpreted with caution. Especially in relation to what are primarily internal experiences of participants, other-report is susceptible to some distortion, and this may be particularly likely if caregivers and FXTAS patients are not getting along. Even among health care providers, many either do not know about, or misunderstand, the behaviors they observe that are associated with the dysexecutive syndrome. The fact that the results for both the SCL-90-R and NPI have a good deal of overlap gives us some confidence, although again, the same caregiver was the informant for both measures.

Summary—The results of this study clarify the psychiatric phenotype of male carriers of the fragile X premutation, especially those with FXTAS, in several important ways. First, psychiatric symptoms appear to be not only more prevalent among men with FXTAS than among controls, but they are more often clinically meaningful. This disorder appears to be dominated by depression, apathy, anxiety, agitation, and behavioral symptoms. Second, the findings suggest that asymptomatic male carriers do not have a markedly elevated risk of significant psychiatric symptoms. However, as the SCL-90-R and NPI do not provide a lifetime prevalence of psychiatric problems, measures that assess psychiatric functioning over a longer interval, such as the Structured Clinical Interview for DSM-IV (SCID), may reveal higher rates of psychopathology in those individuals. Finally, and importantly, the results of this study provide evidence that many emotional and behavioral problems afflicting men with FXTAS are associated with a disturbance of executive functioning. There is a cluster of phenomena that may be related to one another, including depression, hostility, and irritability, in association with behavioral and attentional disinhibition. This suggests that the dysexecutive syndrome associated with FXTAS (Grigsby et al., 2008) may have a significant influence on the psychiatric phenotype.

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Table 1

Participant Characteristics by Group [a]

	FXTAS (*n* = 43)	Asymptomatic Premutation (*n* = 32)	Control (*n* = 37)
Demographics			
Age	68.7 *	59.8	63.5
Years of Education	15.4 °	15.8	16.7
White (%)	100.0%	100.0%	94.3%
Non-Hispanic (%)	95.4%	96.9%	97.1%
Neuropsychological Test Scores	**Mean (SD)**		
Behavioral Dyscontrol Scale	15.9 (5.1) †	20.2 (3.9)	21.8 (3.2)
Mini-Mental State Exam	27.6 (2.5) †	29.3 (0.9)	29.3 (1.1)
Purdue Pegboard –Dominant Hand	8.2 (2.6) †	12.0 (2.0)	12.2 (2.0)

[a] Note. Table 1 presents unadjusted means/rates for participants in the three study groups. For each premutation carrier group, demographic characteristics are compared to the control group by one-way ANOVA.

† $p < 0.001$,

° < 0.10,

* $p \leq 0.05$

Table 2

SCL-90-R: Mean T-Scores (Standard Deviation) and Percentage of Participants with Clinically Significant Symptoms (T-Score ≥ 63) by Group[a]

	FXTAS (N=43)		Asymptomatic Carrier (N=27)		Control (N=35)	
	Mean (SD)	**% in Clinical Range**	**Mean (SD)**	**% in Clinical Range**	**Mean (SD)**	**% in Clinical Range**
Somatization	59.3 (13.7)	44.2**	44.8 (10.2)	7.4	46.7 (13.4)	11.4
Obsessive-Compulsive	60.1 (13.9)	48.8**	47.4 (10.4)	7.4	48.2 (12.1)	11.4
Interpersonal Sensitivity	51.9 (14.2)	25.6	44.8 (12.0)	7.4	45.1 (13.6)	11.4
Depression	59.2 (15.5)	48.8**	41.5 (12.4)	3.7†	47.2 (13.7)	17.1
Anxiety	53.5 (13.0)	32.6*	44.0 (10.9)	3.7	43.3 (12.0)	5.7
Hostility	53.7 (13.3)	27.9	43.1 (9.7)	3.7	44.8 (13.3)	14.3
Phobic Anxiety	47.2 (15.4)	23.3†	38.9 (6.9)	3.7	40.3 (9.7)	5.7
Paranoid Ideation	48.7 (13.2)	14.0	41.5 (9.0)	0.0	43.1 (13.8)	11.4
Psychoticism	53.5 (14.3)	34.9*	42.7 (10.0)	3.7	44.6 (13.5)	11.4
Global Severity Index	58.8 (14.1)	44.2*	43.5 (11.8)	3.7	44.9 (14.9)	14.3
Positive Symptom Distress Index	60.2 (9.6)	41.9**	48.6 (9.6)	11.1	48.1 (10.6)	11.4
Positive Symptom Total	55.8 (12.0)	32.6*	43.4 (10.1)	0.0	44.7 (12.3)	11.4
Number of Dimensions in Clinical Range	3.0 (3.1)**	---	0.4 (1.1)	---	1.0 (2.3)	---
Caseness	---	53.5***	---	11.1	---	17.1

[a]Note. Table 2 presents the mean score (with standard deviation) and the percentage of participants demonstrating clinically significant symptoms, by group, for each SCL-90-R dimension and overall score. The percentage of participants meeting criteria for caseness also is presented. Significance values represent the results of regression models examining the degree to which men with FXTAS or asymptomatic carriers differed from the control group.

† $p \leq 0.10$,

* $p \leq 0.05$,

** $p \leq 0.01$,

*** $p \leq 0.001$

Table 3

NPI: Mean Scores (Standard Deviation) and Percentage of Participants with Clinically Significant Symptoms by Group

	FXTAS (N=39)		Asymptomatic Carrier (N=20)		Control (N=32)	
	Mean (SD)	**% in Clinical Range**	**Mean (SD)**	**% in Clinical Range**	**Mean (SD)**	**% in Clinical Range**
Delusions	0.4 (1.2)	5.1	0.2 (0.9)	5.0	0.4 (2.1)	3.1
Hallucinations	0.1 (0.5)	0.0	0.0 (0.0)	0.0	0.0 (0.0)	0.0
Agitation/Aggression	1.8 (2.8)	23.1 *	0.2 (0.5)	0.0	0.4 (2.1)	3.1
Depression/Dysphoria	2.2 (3.1)	23.1 †	0.9 (2.5)	10.0	0.5 (1.3)	6.2
Anxiety	2.2 (3.4)	25.6 *	1.2 (3.1)	10.0	0.4 (1.3)	6.2
Elation/Euphoria	0.0 (0.0)	0.0	0.0 (0.0)	0.0	0.0 (0.0)	0.0
Apathy/Indifference	3.5 (4.3)	39.5 **	0.8 (2.5)	10.0	0.2 (0.8)	3.1
Disinhibition	1.5 (2.5)	12.8	0.7 (2.2)	10.0	0.3 (1.6)	3.1
Irritability	3.4 (3.9)	36.8 **	1.3 (2.7)	20.0	0.5 (1.6)	6.2
Aberrant Motor Behavior	0.6 (1.8)	7.7	0.0 (0.0)	0.0	0.0 (0.0)	0.0
Nighttime Behavior Problems	2.1 (3.6)	30.8 *	0.7 (2.2)	10.0	0.7 (2.0)	9.4
Appetite/Eating Changes	1.3 (3.2)	15.4	0.0 (0.0)	0.0	0.5 (2.2)	6.2
Total Score Reflects Clinically Significant Disturbance	19.1 (16.8)	79.5 ^	5.9 (12.5)	25.0	3.9 (12.1)	15.6
Number of Domains in Clinical Range	2.2 (2.0) ***	---	0.8 (1.6)	---	0.5 (1.5)	---

Note.

† p ≤ 0.10,

* p ≤ 0.05,

** p ≤ 0.01,

*** p ≤ 0.001,

^ p ≤ 0.0001

Table 4

Mediation Analysis: Indirect Effect of Executive Functioning on NPI and SCL-90-R Variables

Dependent Variable	Significant	Indirect Effect	LL 95%CI	UL 95%CI
Neuropsychiatric Inventory (NPI)				
Fq Delusions	**+**	**0.120**	**0.015**	**0.353**
Sv Delusions	**+**	**0.138**	**0.020**	**0.375**
Fq Hallucinations	**+**	**4.587**	**2.421**	**7.360**
Sv Hallucinations	**+**	**4.587**	**1.853**	**7.199**
Fq Agitation/Aggression	—	0.123	−0.111	0.446
Sv Agitation/Aggression	—	0.072	−0.058	0.268
Fq Depression	**+**	**0.316**	**0.089**	**0.670**
Sv Depression	**+**	**0.163**	**0.043**	**0.407**
Fq Anxiety	—	0.170	−0.037	0.484
Sv Anxiety	—	0.060	−0.106	0.307
Fq Apathy/Indifference	**+**	**0.391**	**0.119**	**0.794**
Sv Apathy/Indifference	**+**	**0.251**	**0.087**	**0.490**
Fq Disinhibition	—	0.085	−0.026	0.213
Sv Disinhibition	**+**	**0.196**	**0.056**	**0.432**
Fq Irritability	**+**	**0.316**	**0.096**	**0.640**
Sv Irritability	**+**	**0.229**	**0.072**	**0.514**
Fq Aberrant Motor Behavior	—	0.140	−3.013	6.770
Sv Aberrant Motor Behavior	—	−0.016	−0.106	0.052
Fq Nighttime Behaviors	**+**	**0.246**	**0.032**	**0.649**
Sv Nighttime Behaviors	—	0.093	−0.023	0.267
Fq Appetite/Eating Behavior	—	−0.016	−0.200	0.142
Sv Appetite/Eating Behavior	—	−0.021	-0.160	0.081
Symptom Checklist 90-R (SCL-90-R)				
Somatization	—	0.027	−0.071	0.146
Obsessive-Compulsive	**+**	**0.120**	**−0.006**	**0.321**
Interpersonal Sensitivity	—	0.076	−0.016	0.254
Depression	**+**	**0.114**	**0.010**	**0.289**
Anxiety	—	0.030	−0.016	0.086
Hostility	**+**	**0.106**	**0.010**	**0.264**
Phobic Anxiety	—	0.044	−0.020	0.162
Paranoia	—	0.074	−0.010	0.261
Psychoticism	**+**	**0.080**	**0.003**	**0.217**
Global Severity Index	—	0.072	−0.010	0.201
Positive Symptom Distress	**+**	**0.100**	**0.009**	**0.236**
Positive Symptom Total	—	1.927	−0.708	6.372

Note. Fq = Frequency, Sv = Severity, Bold font indicates that the 95% Confidence Interval (CI) does not contain zero and is therefore significant.