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Psychiatric symptoms in boys with fragile X syndrome: A comparison with nonsyndromic autism spectrum disorder

Angela John Thurman [a,b,*], Andrea McDuffie [a,b], Randi Hagerman [a,c], Leonard Abbeduto [a,b]

[a] MIND Institute, University of California, Davis, United States
[b] Department of Psychiatry and Behavioral Sciences, University of California, Davis, United States
[c] Department of Pediatrics, University of California, Davis, United States

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ABSTRACT

In the present study, we examined the profile of psychiatric symptoms in boys with fragile X syndrome (FXS) using a parent report instrument. In addition, by comparing boys with FXS to boys with nonsyndromic autism spectrum disorder (ASD) utilizing multiple matching strategies, we examined between-group differences in the types of psychiatric symptoms observed and in the strength of their concurrent associations. Across all matching strategies, symptoms of manic/hyperactive behaviors and general anxiety were more frequently reported for boys with FXS than for boys with nonsyndromic ASD. Results also indicated a positive association between social avoidance and general anxiety in FXS that was stronger than that observed in nonsyndromic ASD across all matching strategies. Theoretical and treatment implications are discussed.

1. Introduction

Fragile X syndrome (FXS) is the leading inherited cause of intellectual disability (Crawford, Acuña, & Sherman, 2001) and is the second only to Down syndrome as a genetic cause of intellectual disability. The syndrome results from an expansion of the cytosine-guanine-guanine (CGG) sequence of nucleotides within the *FMR1* gene on the X chromosome to more than 200 repeats (Oostra & Willemson, 2003). This expansion typically leads to the reduction or absence of FMRP, the protein normally produced by the *FMR1* gene, which is essential for synaptic plasticity and experience-dependent learning (Bassell & Warren, 2008). In addition to cognitive impairments, a variety of behavioral difficulties have a high comorbidity with FXS, especially in males, including hyperactivity and attentional difficulties (e.g., Baumgardner, Reiss, Freund, & Abrams, 1995; Cornish, Scerif, & Karmiloff-Smith, 2007; Scerif, Longhi, Cole, Karmiloff-Smith, & Cornish, 2012; Turk, 1998) and anxiety and withdrawal (e.g., Bregman, Leckman, & Ort, 1988; Cordeiro, Ballinger, Hagerman, & Hessl, 2011; Kau, Reider, Payne, Meyer, & Freund, 2000). Moreover, the vast majority of males with FXS are likely to display some behaviors that are characteristically observed in individuals with nonsyndromic autism spectrum disorder (ASD), that is, individuals with ASD for whom there is no known etiology (Bailey et al., 2004; Baumgardner et al., 1995; Hartley et al., 2011). In the present study, we sought to clarify the behavioral symptom profile of FXS and understand the ways in which this profile is similar to and different from

* Corresponding author at: MIND Institute, Department of Psychiatry and Behavioral Sciences, UC Davis, 2825 50th Street, Room 2101, Sacramento, CA 95817, United States.
E-mail address: angela.thurman@ucdmc.ucdavis.edu (A.J. Thurman).

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that of nonsyndromic ASD. Such data are critical to efforts to develop targeted treatments, especially those that have utility for both FXS and nonsyndromic ASD. Given the moderating effects of the second unaffected X chromosome in females, males with FXS are typically more severely affected across domains of behavioral functioning (Mazzocco, 2000). Thus, the present study focused on males only.

Recent advances in neurobiology have increased our understanding of the pathophysiology of FXS, leading to the development of pharmacological treatments targeting core deficits of this disorder. Such treatments have been shown to rescue many phenotypic features in the *FMR1* knock out (KO) mouse and other animal models of FXS (Bagni, Tasonne, Neri, & Hagerman, 2012; Berry-Kravis et al., 2011; Bhakar, Dölen, & Bear, 2012; Dölen, Carpenter, Ocain, & Bear, 2010; Hagerman, Lauterborn, Au, & Berry-Kravis, 2012). Positive effects of several pharmacological agents have been observed in human clinical trials as well, including those involving minocycline (Dziembowska et al., 2013; Leigh et al., 2013), sertraline (Indah Winarni et al., 2012), AFQ056 (an mGluR5 antagonist) (Jacquemont et al., 2011), and arbaclofen (a $GABA_B$ agonist) (Berry-Kravis et al., 2012). More generally, the symptom overlap between FXS and nonsyndromic ASD has led to the hope that targeted treatments benefitting FXS will also benefit those with nonsyndromic ASD (Gurkan & Hagerman, 2012). Despite initial positive results and the optimism generated among scientists and families, there have been many disappointments in human clinical trials as well. In general, results for humans with FXS have been modest relative to the impressive findings with the KO mouse. Moreover, the extension of drugs with positive findings for FXS to individuals with nonsyndromic ASD has not always shown benefit, with arbaclofen being a recent high-profile "failure" for nonsyndromic ASD (Pollack, 2013).

There are several reasons for the pattern of human study findings. First, although the impairments that define FXS have been well described for many behavioral domains, there remains much that we do not understand about the phenotype, including the extent to which different behavioral symptoms associated with the FXS phenotype emerge from the same or different underlying neural mechanisms. As a result, decisions about which behavioral endpoints to select for use in clinical trials have often been based on clinical intuition rather than being hypothesis driven. It would be useful, therefore, to understand which symptoms of the FXS phenotype are strongly correlated with one another, which would suggest common underlying mechanisms, and which symptoms are not correlated, which would suggest different underlying mechanisms. Second, despite the findings of shared behavioral symptoms between FXS and nonsyndromic ASD, there is emerging evidence suggesting that the same behavioral symptoms may reflect different underlying mechanisms in the two conditions (Gallagher & Hallahan, 2012; McDuffie, Thurman, Hagerman, & Abbeduto, in press; Wolff et al., 2012). If this is the case, the expectation of finding targeted treatments that are equally efficacious across the disorders might not be reasonable. Direct studies comparing behavioral profiles across FXS and nonsyndromic ASD have been few and existenting studies do not adequately account for other developmental characteristics that differ between the two disorders, such as IQ, which can complicate interpretation of such cross-syndrome comparisons.

The current study was designed to compare the behavioral profiles observed in FXS to the profiles observed in nonsyndromic ASD. To begin to identify characteristics that may be unique to the behavioral phenotype associated with FXS, we examined the psychiatric symptom profile of boys with FXS relative to comparison groups of same-aged children with a diagnosis of nonsyndromic ASD. In the present study, we use the term "nonsyndromic ASD" to refer to boys who display symptoms of autism that are frequent and/or severe enough to exceed behavioral criteria for a research classification of ASD, but for whom a comorbid genetic diagnosis of FXS or other known etiology has been ruled out. To inform our understanding of whether the same behavioral symptoms reflect similar or different underlying psychological mechanisms, we examined concurrent associations across domains of psychiatric symptoms as well as concurrent associations between these symptoms and other domains of functioning across the two disorders. Studies such as these are vital to understanding the extent to which targeted treatments may be similarly efficacious in FXS and nonsyndromic ASD.

1.1. Symptoms associated with an autism spectrum disorder

Behavioral characteristics typically associated with the presentation of an ASD are frequently observed in males with FXS. As many as 90% of males with FXS are described as displaying at least some behavioral symptoms of an ASD; furthermore, when utilizing standard caseness criteria for research classification of ASD (Risi et al., 2006), it is estimated that 60% of males with FXS have symptoms that are frequent and severe enough to warrant a comorbid diagnosis of ASD (e.g., Harris et al., 2008). Despite these findings, there is disagreement regarding how to interpret the presence or absence of behaviors typically associated with a classification of ASD in the context of an individual with FXS. Currently, there is much debate within the field regarding whether the behavioral symptoms typically interpreted to represent core domains of autism symptomatology are: (1) the result of the same underlying neurological/psychological impairments that affect individuals with nonsyndromic ASD or (2) superficially similar behaviors but arise from different underlying psychological/neurological impairments. Given recent findings of neuroimaging studies suggesting potentially important structural and functional differences between the brains of individuals with FXS and those with nonsyndromic ASD (for review see Gallagher & Hallahan, 2012), research focused on elucidating the similarities and differences between the two disorders and examining at what levels these differences exist is of particular importance. Direct comparisons between appropriately matched FXS and ASD samples are necessary to discern where the behavioral and neurophysiological boundaries lay between these two disorders.

To date, many comparisons between individuals with FXS and individuals with nonsyndromic ASD have focused on the behaviors central to a diagnosis of ASD, examined as either a function of symptom severity and/or categorical diagnostic metrics. Recent findings have begun to identify between-syndrome differences between boys with FXS and boys with