Title: The Impact of Mental Age on ADHD Diagnosis in Preschoolers with Fragile X Syndrome and Autism Spectrum Disorder

Authors: Shannon L. O’Connor¹, Kimberly J. Hills¹, Elizabeth A. Will³, and Jane E. Roberts¹
¹University of South Carolina

Introduction: Attention Deficit/Hyperactivity Disorder (ADHD) is the most commonly diagnosed behavioral disorder in children, with about 11% of the general population receiving a diagnosis of ADHD (Kessler et al., 2006). Symptoms of ADHD, such as inattention, hyperactivity and impulsivity, are elevated in children with fragile X syndrome (FXS) and autism spectrum disorder (ASD). In children with FXS, between to 53% to 84% exhibit symptoms of ADHD (Bailey, Raspa, Olmsted, & Holiday, 2008; Sullivan et al., 2006) and between 37% and 85% of children with ASD exhibit symptoms of ADHD (Leitner, 2014). The phenotype of each of these disorders also includes the presence of intellectual disability (ID; Schneider, Hagerman, & Hessl, 2009; Baio, et al., 2018), with a majority of individuals with FXS also having ID and approximately 40% of individuals with ASD also having ID. The presence of ID can pose challenges for differential diagnosis of co-occurring disorders such as ADHD. The relation between ADHD and ID is complicated by the fact that both disorders share a number of overlapping symptoms. Research has shown that individuals with ID are at increased risk for development of ADHD. Most studies demonstrate that ADHD can be differentiated in the presence of ID as a distinct pathology from the phenotype of non-syndromic ID (Hastings, Beck, Daley, & Hill, 2005; McClain, Hasty Mills, & Murphy, 2017; Neece, Baker, Blacher, & Crnic, 2011). However, when also considering the presence of additional disorders such as ASD, diagnostic certainty of ADHD decreases, also due to the high symptom overlap between ASD and ADHD (Stevens, Peng, & Barnard-Brak, 2016). The presence of multiple comorbid disorders in both FXS and ASD further complicates the ability to differentially diagnose disorders which can lead to significantly worse outcomes than individuals with FXS or ASD only (Thurman, McDuffie, Hagerman, & Abbeduto, 2014). Additionally, many individuals with ID are non-verbal, and unable to report on their own behaviors and experiences, thus making parent report the most viable option to measure the presence of co-occurring symptoms. The present study contrasts the rate of ADHD diagnosis using a structured clinical parent interview, before and after accounting for the presence of ID in preschoolers with FXS compared to preschoolers with ASD.

Method: Participants included 26 preschool aged males with FXS ($M_{age} = 46.65, SD = 11.07$) and 22 male preschoolers with ASD ($M_{age} = 43.77, SD = 6.61$). The groups were not significantly different on either chronological age [$F(1) = 1.14, p = .290$] or mental age [$F(1) = .663, p = .420$], with mean mental age estimates of $54.05 (SD = 8.19)$ for the FXS group and $56.81 (SD = 10.05)$ for the ASD group. Verbal mental age estimates were derived using an average of the receptive and expressive subscales and overall developmental level/ID was represented by the Early Learning Composite of the Mullen Scales of Early Learning (MSEL; Mullen, 1995). Mullen ELC scores were not included in analyses beyond age matching. The Autism Diagnostic Observation Schedule, Second Edition (ADOS-2; cite) was administered to confirm ASD diagnoses in the ASD group and consider the presence of ASD in the FXS group. To diagnose ADHD, trained interviewers used the Preschool Age Psychiatric Assessment (PAPA; Egger et al., 2006), to conduct structured clinical interview that measures psychiatric symptoms in two to five-year-olds. The PAPA, which uses a DSM-based format, was included in a clinical best estimate (CBE) process to determine diagnostic status across autism, ADHD, and anxiety. Through the CBE process, examiners and a licensed psychologist reviewed participant videos, endorsement of psychopathology domains (including ADHD and ASD), and measures of overall developmental status and adaptive behavior to make diagnostic determinations. Additionally, when considering diagnoses in participants with FXS, the presence of ASD is considered prior to making any determinations. Diagnostic rates were obtained from the PAPA before and after the CBE process to determine the impact of ID on the diagnosis of ADHD in children with FXS and ASD.

Result: First, we took a descriptive approach (i.e. frequency distributions) to assess the rates of ADHD diagnosis in each group. Rates were taken from the PAPA and calculated without the consideration of mental age and with the consideration of mental age. Thus, resulting in two sets of diagnostic rates (pre-mental age and post mental age) for each group. These rates can be found in Table 1. Second, after calculating the diagnostic frequency distributions for each group, between group analyses were conducted to examine the differences in rates of ADHD between the FXS and ASD groups. Last, we examined the differences in rates pre and post consideration of mental age within each group. To accomplish these comparisons, we ran chi-squared analyses. These results may also be found in Table 1.
Table 1.

<table>
<thead>
<tr>
<th></th>
<th>PAPA only Diagnosis (pre-mental age consideration)</th>
<th>PAPA + CBE Diagnosis (with mental age consideration)</th>
<th>Difference in rates pre and post mental age consideration (within groups)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FXS</td>
<td>26.9%</td>
<td>23.1%</td>
<td>$X^2(1) = 0.102, p = .748$</td>
</tr>
<tr>
<td>ASD</td>
<td>36.3%</td>
<td>4.5%</td>
<td>$X^2(1) = 6.84, p = .001$</td>
</tr>
<tr>
<td>Difference between FXS and ASD Rates</td>
<td>$X^2(1) = 0.494, p = .482$</td>
<td>$X^2(1) = 3.28, p = .070$</td>
<td>---</td>
</tr>
</tbody>
</table>

**Discussion:** Overall, rates from the present study are somewhat lower than previously identified rates of ADHD in individuals with FXS and ASD, yet, still exceed rates found in the general population. This is likely due to the age of participants in the present study and is consistent with previous findings that ADHD increases over time in preschoolers with FXS (Grefer, Flory, Cornish, Hatton, & Roberts, 2016). When testing differences in diagnostic rates, no significant differences were found between groups, either before (PAPA only) or after (PAPA+CBE) considering mental age. When testing differences in diagnostic change within groups from pre- and post-mental age consideration, no significant differences were found within the FXS group. This may support previous findings that ADHD is a distinct diagnosis in individuals with syndromic ID. However, in the ASD group there was a significant drop in diagnostic rates when considering mental age, implying that behaviors attributable to ADHD in this group, more likely were accounted for by the presence of ID or the primary diagnosis of ASD. This finding contradicts previous findings that ADHD is a distinct diagnosis in both non-syndromic ID and syndromic ID. Additionally, these results justify the use of the PAPA as a measure of ADHD in individuals with FXS and ASD.

**References/Citations:**