Cognitive, language and social-cognitive skills of individuals with fragile X syndrome with and without autism

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Abstract

Background It is not known whether those with co-morbid fragile X syndrome (FXS) and autism represent a distinct subtype of FXS; whether the especially severe cognitive delays seen in studies of young children with co-morbid FXS and autism compared with those with only FXS continue into adolescence and young adulthood; and whether autism in those with FXS is ‘true autism’, i.e. reflects the same underlying problems as idiopathic autism.

Method We compared the non-verbal IQ of adolescents and young adults with co-morbid FXS and autism (n = 10) with those with only FXS (n = 44). We then created a subsample of those with FXS only, matched on non-verbal IQ, mental age and gender (n = 21) to the subsample of those with co-morbid FXS and autism. We compared the two groups on measures of expressive language, receptive language (lexical, grammatical morphology and syntactic patterns), and a theory of mind task.

Results Those with co-morbid FXS and autism had lower non-verbal IQs than those with only FXS. The participants with co-morbid FXS and autism did not perform as well as the cognitive ability- and gender-matched participants with only FXS on the three measures of receptive language or the theory of mind task; there were no differences on the expressive language measure.

Conclusions Our findings support the notion that those with co-morbid FXS and autism represent a distinct subtype of FXS, with more impairment in receptive language and theory of mind even when controlling for their lower non-verbal IQ relative to those with only FXS. The greater cognitive impairments observed in those with co-morbid FXS and autism continues into adolescence and young adulthood; and the autism seen in those with FXS appears to be the same as idiopathic autism.

Keywords autism, behavioural phenotypes, cognitive behaviour, communication, fragile X, intellectual disability

Introduction

The association between fragile X syndrome (FXS) and autism has been well documented (Hagerman 1999; Dykens et al. 2000; Feinstein & Reiss 2001; Bailey et al. 2004). Several studies, involving more than 200 participants, have yielded prevalence rates of autism in FXS from 0 to 50% (Demark et al. 2003), with a consensus of 25% to 30% (Bailey et al. 2004). The link between the two disorders is further established by studies of the prevalence of FXS in autism (Dykens & Volkmar 1987; Demark et al. 2003), which have yielded rates of FXS of 0% to 16%, with a generally agreed-upon rate of 4% to 5%
(Brown et al. 1982; Fisch 1992; Demark et al. 2003). Nevertheless, there is much that is not known about the co-morbidity of these two conditions and thus, considerable controversy about how best to conceptualize the distinction between those with FXS who do and do not meet diagnostic criteria for autism (Bailey et al. 2004). In the study reported here, we addressed the controversy by further differentiating the behavioural phenotypes of these two groups of youth with FXS.

The controversy concerning the expression of autism in FXS is focused largely on two issues. First, there is a debate as to whether the autistic symptomatology in FXS represents a continuum, with only the most severely affected reaching the ‘threshold’ for a diagnosis of autism, or whether those with and without autism represent two, qualitatively distinct, subtypes of FXS (Rogers et al. 2001; Bailey et al. 2004; Kau et al. 2004; Kaufmann et al. 2004; Philofsky et al. 2004). In the former case, the claim is that FXS is associated with variable expression on multiple behavioural continua, from the cognitive to the social-affective, and that autism is just variation on the social-affective continuum. The contrasting claim is that autism and FXS are two distinct disorders that have an ‘affinity’ for co-occurrence and thus, those with FXS with and without autism are categorically, rather than quantitatively, different. Second, there is a debate as to whether the mechanisms underlying autistic behaviour are the same in FXS and idiopathic cases of autism. It has been suggested, for example, that autistic symptomatology arises from social anxiety in FXS and from social indifference in idiopathic autism (see Bailey et al. 2004 for a review).

In the study reported here, we addressed these controversies by expanding our understanding of the variability in the behavioural profile of individuals with FXS who do or do not meet criteria for autism. We compared individuals with FXS with and without autism in the domains of non-verbal cognition, receptive and expressive language, and social cognition, specifically theory of mind. We reasoned that if individuals with FXS with and without autism represented distinct subtypes, they should differ in their profiles of strengths and weaknesses in these domains. We also reasoned that if autism in FXS and in idiopathic (non-FXS) cases result from the same underlying mechanisms, the profile we observe in individuals with both FXS and autism should be similar to the profile typically observed in idiopathic autism.

Cognition

Several recent studies suggest that young boys with FXS who meet criteria for autism are more cognitively impaired than those with only FXS or only autism (Bailey et al. 2001; Kau et al. 2004; Kaufmann et al. 2004; Philofsky et al. 2004). In many instances, however, the studies were not specifically designed to compare the level of cognitive impairment across the samples. Moreover, numerous methodological limitations require that the results of these studies be interpreted cautiously. These limitations include the use of ratio IQs, which are fraught with interpretive problems (Sattler 2001), in several studies (Kau et al. 2004; Kaufmann et al. 2004). Previous studies are also limited by the use of full-scale IQ scores or Batelle Developmental Inventory (Newborg et al. 1984) cognitive scores that conflate verbal and non-verbal performance (Bailey et al. 2001; Kau et al. 2004; Kaufmann et al. 2004). This makes it difficult to know whether the findings reflect greater cognitive affectedness in individuals with both FXS and autism compared with those with only FXS, or whether the findings reflect simply the ‘typical’ profile of autism (i.e. especially severe impairments in some aspects of language). It is also problematic that different intelligence tests have been administered across individuals within some studies (Kau et al. 2004; Kaufmann et al. 2004), which is likely to obscure the true relationship between IQ and autism symptoms. Other limitations include the use of different methods for diagnosing autism across studies and the inclusion of Pervasive Developmental Disorder – Not Otherwise Specified (PDD-NOS) within the autism group in some studies (Bailey et al. 2001) but not in others (Kau et al. 2004; Kaufmann et al. 2004; Philofsky et al. 2004), which makes cross-study comparisons difficult.

In contrast to studies of young boys with FXS, studies with age ranges extending from early childhood into middle adulthood are less consistent in finding lower IQs in individuals with FXS who also have autism than in those without autism. Reiss & Freund (1990), whose 17 participants ranged from 3 to 24 years of age, found no relationship between Verbal or Composite IQ on the Stanford-Binet, 4th
In a more recent study, Cohen (1995) found that IQ was 20 points lower and statistically different in 2- to 21-year-olds who had co-morbid FXS and autism (n = 7) compared with those with only FXS (n = 25). The small sample size, variability in the tests used to measure cognition across participants, and the failure to distinguish between verbal and non-verbal cognitive tests suggest the need for replication.

In summary, there is evidence for a greater cognitive delay in those with co-morbid FXS and autism relative to those with only FXS; however, this finding is more robust in studies that have focused exclusively on children. In studies with age ranges extending from early childhood into middle adulthood, the findings are less consistently in support of lower IQ in individuals with FXS who also have autism than in those without autism. It is possible therefore that the difference in severity of cognitive impairments between those with FXS with and without autism diminishes with age. Methodological limitations in previous studies, however, suggest the need for further research on individuals beyond childhood.

In the present study, we examined differences in cognitive functioning between those with FXS with and without a co-morbid diagnosis of autism over the age period of early adolescence to young adulthood, using the same procedures across participants for diagnosing autism and measuring cognitive ability. A non-verbal measure of cognitive ability was used to avoid confounding IQ [and mental age (MA)] with language skills.

Receptive language

Although impaired receptive language is not a diagnostic criterion for autistic disorder, impairments in receptive language in excess of that expected based on non-verbal cognition are frequently seen in that population (Gillum & Camarata 2004). Moreover, the Diagnostic and Statistical Manual of Mental Disorders – 4th edition (DSM-IV; published by the American Psychiatric Association 1994) notes that as an associated feature, the level of receptive language is lower than that of expressive language in many high-functioning children with autism. In FXS, however, receptive language is not more impaired than non-verbal intelligence in adolescents and young adults, at least not in individuals without a co-morbid diagnosis of autism (Abbeduto et al. 2003).

There are three studies in which receptive language in youth with co-morbid FXS and autism has been compared with that in those with only FXS. Using the Reynell Developmental Language Scales (Reynell & Huntley 1971), Roberts et al. (2001) found lower receptive language scores in boys between 20 and 86 months with co-morbid FXS and autism compared with those with only FXS, even after adjusting for scores on the cognitive portion of the Battelle Developmental Inventory (Newborg et al. 1984). In a study of boys aged 22–45 months, Philofsky et al. (2004) found receptive language, measured using the Receptive Language subscale of the Mullen Scales of Early Learning (Mullen 1995), to be especially weak in those with co-morbid autism and FXS; however, these investigators did not control for level of non-verbal cognition, which was significantly lower in the co-morbid autism and FXS group. In contrast, Kaufmann et al. (2004) found no relationship between the severity of autistic symptoms, based on the Autism Diagnostic Interview – Revised (ADI-R, Lord et al. 1994) and receptive language scores based on the Preschool Language Scales – 3rd edition (PLS-3, Zimmerman et al. 1992), in boys 3 to 8 years of age.

In addition to a lack of consistency in findings, the studies conducted to date have focused only on young children and have included relatively few participants in the sample with co-morbid FXS and autism. Thus, there is a need for additional data on receptive language differences between individuals with FXS with and without co-morbid autism,
especially for older individuals, so that we can determine the extent to which the differences in receptive language between those with and without co-morbid autism extend into adolescence and beyond. Moreover, there is a need to control for differences in non-verbal cognitive ability in any such comparison. Additionally, it should be noted that studies to date have used rather gross measures of receptive language that fail to discriminate, for example, between limitations in vocabulary and syntax. In the present study, data on receptive language were collected for those with only FXS and those with co-morbid FXS and autism. We also controlled for differences in non-verbal IQ and MA in this comparison, and used a measure that allowed us to examine the syntactic, lexical and morphological components of receptive language.

Expressive language

Delays in the development of expressive language are frequent in both idiopathic autism (Tager-Flusberg 2001a) and FXS without autism (Murphy & Abbeduto 2003). Studies of the relationship of expressive language in autism within FXS, however, have yielded a confusing pattern of findings. Roberts et al. (2001) found that the presence of autistic symptoms, based on the Childhood Autism Rating Scale (CARS, Schopler et al. 1988) was associated with marginally ($P = 0.06$) lower expressive language scores (on the Reynell) in boys 20–86 months. In a similar vein, Bailey et al. (2001) found that 2- to 7-year-old boys with co-morbid FXS and autism (based on a score of 30 or above on the CARS) had significantly lower expressive language scores and progressed at significantly slower rates in expressive language than did boys with only FXS. In contrast, Kaufmann et al. (2004) found that higher expressive language scores from the PLS-3 were related, surprisingly, to higher ADI-R scores (i.e. more severely autistic behaviour) in 3- to 8-year-old boys with FXS.

The inconsistent findings for expressive language may indicate that differences in expressive language between individuals with FXS with and without co-morbid autism are of less magnitude or less pervasive than is the case for receptive language impairments. In light of the limited research in this area, however, it would be useful to have additional data on expressive language, especially within a study in which both expressive and receptive measures were administered to participants. Moreover, it would again be important to extend the age range, as only children were included in the studies of Bailey et al. (2001), Roberts et al. (2001) and Kaufmann et al. (2004). In the present study, data on expressive language were collected, in addition to those on receptive language and non-verbal cognition.

Theory of mind

Impairments in theory of mind appear to distinguish individuals with idiopathic autism from individuals with FXS without autism. Theory of mind refers to the conceptual system used to reason about beliefs, emotions and other mental states (Baron-Cohen et al. 1993; Karmiloff-Smith et al. 1995; Frith 1996). A foundational achievement in acquiring a theory of mind is the understanding of the mind’s representational nature (Perner 1988). This understanding typically emerges in primitive form near age 4 years, and is manifested in, among other things, the child’s facility with reasoning about false belief (i.e. recognition that another person may hold a belief different from the child’s own). Those with autism typically do poorly on belief tasks, even relative to their level of intellectual functioning (Baron-Cohen et al. 1985; Baron-Cohen 1989; Tager-Flusberg & Sullivan 1994; Yirmiya et al. 1998). In contrast, individuals with FXS, at least those without a co-morbid autism diagnosis, display levels of accuracy on such tasks that are closer to their level of intellectual functioning and superior to the performance of individuals with idiopathic autism (Garner et al. 1999; Abbeduto & Murphy 2004; Cornish et al. 2005).

There have been no direct comparisons on theory of mind measures between those with and without autism among FXS youth. In light of the central role given to a core deficit in theory of mind in autism by many theorists (e.g. Tager-Flusberg 2001b), data in this domain are critical to our understanding the nature of autism within FXS. In the present study, we measured progress in acquiring a theory of mind by comparing the performance of the two groups of youth with FXS on a false belief task.

Summary

The present study was designed to compare adolescents and young adults with only FXS with those...
with both FXS and autism in the domains of cognition, language and theory of mind, in order to begin to clarify the relationship between these two conditions. Two questions were addressed: (1) Do youth with only FXS differ from those with co-morbid FXS and autism in the severity of their cognitive impairments? (2) Do adolescents with only FXS differ from those with co-morbid FXS and autism in their profile of impairments in the domains of expressive language, receptive language and theory of mind?

Method

Participants

The 54 participants for the present study were drawn from an ongoing project focused on language development in adolescents and young adults with FXS – or Down’s syndrome (Abbeduto et al. 2003; Abbeduto & Murphy 2004). We recruited local families through advertisements in newspapers, mailings to special educators, and through a university registry of families interested in participating in research. Families were also recruited nationally through postings on the Internet and newsletters of nationwide developmental disabilities organizations. Several participants in the present sample were included in the sample described by Abbeduto et al. (2003), which focused on the behavioural development of individuals with FXS without autism.

Copies of reports of DNA confirmation of the fragile X full mutation were available for all but two of the participants. In one case, DNA testing had been conducted, but the report was missing; and in the second case, only cytogenetic testing had been conducted. All participants with FXS with DNA results were found to have the full mutation, although cases of mosaicism (i.e. premutation plus full mutation) were not excluded.

The participants ranged in age from 11.4 to 23.4 years. Forty-two were males. A hearing evaluation indicated that no participant had more than a mild hearing loss, and most had normal range pure-tone thresholds.

Autism status

The autism status of participants in these groups was confirmed by a two-step process. In Step 1, we asked the teacher, the mother and (in two-parent families) the father of each target adolescent and young adult to complete the Autism Behaviour Checklist (ABC) (Krug et al. 1993). The ABC is a commonly used screening measure, on which the informant is asked to indicate which of the common behavioural manifestations of autism the target individual displays. Following Volkmar et al. (1988), we used a score of 44 or higher as reflecting the possible appropriateness of an autism diagnosis. Any participant who met or exceeded this score according to the responses of at least two of the three informants in two-parent families (and either the teacher or the mother in the case of single-parent families) was then referred for further evaluation at Step 2. Although differences in ABC scores among informants are to be expected in light of the different experiences and contexts against which they judge the target youth, there was generally good agreement among informants: Pearson correlations between the ABC scores of pairs of informants were all significant at $P \leq 0.008$ (one-tailed).

In Step 2, referred participants were evaluated by a licensed psychologist at a university-affiliated developmental disabilities clinic. The psychologist (P.L.), who conducted the clinical evaluation, has more than 20 years of experience in the field of autism. She evaluated the referred participants against DSM-IV criteria for autistic disorder. The evaluation took 1.5 to 2 h and consisted of three phases: (1) observation of the individual interacting with his or her parent(s); (2) direct interaction with the individual; and (3) a structured interview with the individual’s parents, covering each of the DSM-IV criteria, as well as the associated features and developmental history. The exact content of each phase varied slightly across participants, in response to individual differences in behaviour elicited and parent-reported history.

In the first phase, the parent or parents were instructed to spend about 10 min with their child, interacting as they typically might. They usually talked or worked a jigsaw puzzle together. In the second phase, which also generally lasted 10 min, the psychologist entered the room, while the parent or parents left. The psychologist interacted with the individual using the same materials as had the parents. She also asked questions about school, such as favourite subjects and teachers. In the final phase, the
A psychologist interviewed the parent(s) regarding DSM-IV criteria, using a set of questions and examples that she had developed in her clinical practice, which were guided by various autism diagnostic instruments and her own experience. Ten of the participants, all males, received a diagnosis of autistic disorder from the psychologist. The characteristics of this subsample of participants with autism are provided in the right-most column of Table 1. A diagnosis of PDD-NOS was not considered; only those who met full criteria for autism were included in the group of those with autism.

We compared characteristics of the subsample with autism with the remaining participants (the FXS only full sample; n = 44), to determine whether the two groups were comparable, so that we could meaningfully compare non-verbal IQ in the two groups. The characteristics of those with only FXS are presented in the left-most column of Table 1. T-tests revealed no significant differences between the autism and FXS only matched subgroups in chronological age or MA (as determined from the Stanford-Binet, 4th edition subtests).\(^1\) Chi-squared tests revealed no significant differences between the autism and FXS only matched subgroups in race (non-white vs. white), relationship to mother (biological vs. non-biological), or mother’s education (college graduate or beyond vs. less than college graduate). At the same time, however, the FXS only matched subsample received lower scores on the ABC than did the subsample with autism [Mother ABC, t (28) = −5.30, \(P \leq 0.0005\); Father ABC, t (46) = −3.60, \(P \leq 0.0005\); Teacher ABC, t (48) = −1.99, \(P = 0.026\), all tests one-tailed].

We also compared the autism subsample with that of non-autistic, gender- and cognitive ability-matched participants (the FXS only matched subsample; n = 21). The latter was created by selecting from the participants without autism only males who received a standard score of 36 (the lowest standard score possible) on the Stanford-Binet subtests, making them identical to the autism subsample in this regard (as described below). The characteristics of the FXS only matched subsample of participants are provided in the middle column of Table 1.

\(^1\) Even among participants achieving a standard score of 36, variations in the number of items answered correctly (and thus, MA) are possible on the Stanford-Binet, 4th edition.

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### Table 1  Participant characteristics

<table>
<thead>
<tr>
<th></th>
<th>Fragile X only full sample</th>
<th>Fragile X only matched subsample</th>
<th>Fragile X with autism subsample</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>44</td>
<td>21</td>
<td>10</td>
</tr>
<tr>
<td>Number of males</td>
<td>32</td>
<td>21</td>
<td>10</td>
</tr>
<tr>
<td>Mean CA in years (SD)</td>
<td>15.7 (2.8)</td>
<td>16.0 (3.3)</td>
<td>16.1 (2.4)</td>
</tr>
<tr>
<td>Mean non-verbal IQ (SD)^*</td>
<td>46.3 (15.6)</td>
<td>36 (0.0)</td>
<td>36 (0.0)</td>
</tr>
<tr>
<td>Mean non-verbal MA in years (SD)^*</td>
<td>5.4 (2.3)</td>
<td>3.8 (0.5)</td>
<td>3.7 (0.5)</td>
</tr>
<tr>
<td>Mother ABC mean (SD)</td>
<td>30.8 (18.0)</td>
<td>34.9 (18.3)</td>
<td>72.2 (18.0)</td>
</tr>
<tr>
<td>Father ABC mean (SD)</td>
<td>28.2 (22.9)</td>
<td>36.9 (26.5)</td>
<td>61.6 (29.6)</td>
</tr>
<tr>
<td>Teacher ABC mean (SD)</td>
<td>26.3 (21.5)</td>
<td>31.7 (19.1)</td>
<td>41.9 (20.4)</td>
</tr>
<tr>
<td>Number of Caucasians</td>
<td>41</td>
<td>20</td>
<td>8</td>
</tr>
<tr>
<td>Number of mothers with college or advanced degrees</td>
<td>26</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>Number of biological mothers</td>
<td>39</td>
<td>18</td>
<td>7</td>
</tr>
</tbody>
</table>

Stanford-Binet, participant by administering three subtests from the Non-verbal IQ and MA were estimated for each participant by administering three subtests from the Stanford-Binet, 4th edition (Thorndike et al. 1986): Copying and Pattern Analysis (from the Abstract Visual Reasoning area of the test) and Bead Memory (from the Short-term Memory area of the test). These subtests measure short-term memory for visuospatial sequences (Bead Memory), the ability to analyse visuospatial patterns (Pattern Analysis), and the ability to reproduce previously seen visuospatial patterns through sensorimotor acts (Copying). These subtests require few verbal instructions to administer and the participant responds non-verbally. IQ was determined according to procedures for calculating partial composites (Thorndike et al. 1986). MA was determined by taking the mean of the age-equivalents for the three subtests following Chapman et al. (1991).

Non-verbal cognition

Non-verbal IQ and MA were estimated for each participant by administering three subtests from the Stanford-Binet, 4th edition (Thorndike et al. 1986): Copying and Pattern Analysis (from the Abstract Visual Reasoning area of the test) and Bead Memory (from the Short-term Memory area of the test). These subtests measure short-term memory for visuospatial sequences (Bead Memory), the ability to analyse visuospatial patterns (Pattern Analysis), and the ability to reproduce previously seen visuospatial patterns through sensorimotor acts (Copying). These subtests require few verbal instructions to administer and the participant responds non-verbally. IQ was determined according to procedures for calculating partial composites (Thorndike et al. 1986). MA was determined by taking the mean of the age-equivalents for the three subtests following Chapman et al. (1991).

Expressive language

Expressive language was assessed by administering the Oral Expression Scale (OES) of the Oral and Written Language Scales (Carrow-Woolfolk 1995). The OES is a standardized test designed to measure numerous dimensions of language expression, from single-word use to connected discourse, although the emphasis is on the mastery of language forms. In administering each item, the experimenter reads aloud a verbal stimulus that requires the participant to answer a question, complete a sentence or generate a new sentence. Accompanying drawings provide contextual support. We computed an OES raw score and age-equivalent score for each participant. Standard scores were not computed, because the norms for the test did not extend low enough to provide discrimination in terms of standard scores among many lower-functioning participants.

Theory of mind

We administered a false belief task that followed the structure of tasks used by many investigators studying theory of mind in typically developing children and developmentally delayed individuals (Yirmiya et al. 1998). Success on such tasks is thought to reflect the recognition that the human mind does not simply copy the world, but rather represents and interprets it (Tager-Flusberg 2001b). This recognition first emerges in typically developing children during the pre-school years, although some complex forms of theory of mind reasoning emerge later and the influence of task variations on that reasoning diminishes with age (Yirmiya et al. 1998).

We assessed reasoning about both first-order false beliefs (i.e. another person’s beliefs about the world) and second-order false beliefs (i.e. another person’s beliefs about what yet another person believes about the world). The assessment procedure was based on that of Tager-Flusberg (Sullivan et al. 1994; Tager-Flusberg & Sullivan 1994). This procedure reduces the linguistic and information processing demands often associated with assessing second-order false beliefs and makes the testing conditions more similar to those for assessing first-order beliefs. As a result, typical children (Sullivan et al. 1994) and the youth with autism or intellectual disability (ID) (Tager-Flusberg & Sullivan 1994) are nearly as...
successful on second-order reasoning as on first-order reasoning.

The examiner told a brief story while enacting it with miniature props. The story involved an object changing location. Some characters held false beliefs about the object’s location (first-order false belief) or about what the other characters believed about the object’s location (second-order false belief). At all times, the participant knew the true location of the object and which characters had and had not witnessed the object’s change of location. Four test questions assessed whether the participant correctly recognized the object’s change of location. The numbers of test and control questions answered correctly were computed. The script for this task is provided as an Appendix.

Procedure

Each participant was tested individually in a quiet laboratory room at a university research centre. The TACL, OES, false belief task and Stanford-Binet, 4th edition subtests were part of a longer research protocol administered across two sessions per participant. The sessions were conducted on different days whenever possible, with the intent being that no more than 2 to 3 weeks separate the sessions for any given participant. If parents felt it appropriate, the sessions were administered on 1 day with a 1- to 2-h break between sessions. For any given participant, the same examiner administered the entire protocol (with the exception of the clinical evaluation for autism, which was conducted by the psychologist, typically on the same day as one of the other testing sessions).

Results

Fragile X syndrome (FXS) only full sample vs. autism subsample

The two groups were compared in terms of non-verbal IQ and MA. A Fisher’s exact test was used to determine whether participants with autism were more likely than participants without autism to receive the lowest standard score possible on the Stanford-Binet, 4th edition subtests (i.e. 36). In fact, only 21 of the 44 participants from the FXS only full sample received this score compared with all 10 of the participants with an autism diagnosis. This was a significant difference (Fisher’s exact test, $P = 0.002$, one-tailed). Similarly, a $t$-test indicated that MA measured from the Stanford-Binet, 4th edition subtests was higher for the FXS only full sample than for the subsample with autism, $t(51.9)$, equal variances not assumed) = 4.39, $P \leq 0.0005$, partial $\eta^2 = 0.09$.

Fragile X syndrome (FXS) only matched subsample vs. autism subsample

We compared the OES scores of the matched subsamples. There were no significant differences between the subsamples on either the raw scores, $t(29) = 1.71, P = 0.10$ (two-tailed), or age-equivalent scores, $t(28) = 0.98, P = 0.34$ (two-tailed). The mean raw scores were 23.9 (SD = 15.2) and 32.0 (SD = 11.0), and the mean age-equivalents were 4.4 (SD = 1.2) and 4.9 (SD = 1.3), for the autism subsample and FXS only matched subsample, respectively.

We also compared the subsamples on their scores on the three TACL-R or TACL-3 subtests, using a repeated-measures ANOVA. The subsample with autism performed significantly more poorly than did the FXS only matched subsample in terms of both their raw scores, $F(1,29) = 5.96, P < 0.02$, partial $\eta^2 = 0.17$, and age-equivalents, $F(1,29) = 5.28, P < 0.03$, partial $\eta^2 = 0.15$. The interaction of subsample and subtest was not significant in either analysis. The mean raw scores on the lexical, grammatical morphology and syntactic patterns portions of the TACL were 23.6 (SD = 4.2), 20.8 (SD = 8.2) and 14.5 (SD = 8.7), respectively, for the subsample with autism and 29.0 (SD = 5.4), 24.4 (SD = 8.5) and 21.3 (SD = 8.7), respectively, for the FXS only matched subsample. The corresponding mean age-equivalent scores on these three subtests were 4.3 (SD = 0.6), 5.2 (SD = 1.1) and 4.4 (SD = 1.1) for the subsample with autism and 5.1 (SD = 0.9), 5.6 (SD = 1.4) and 5.5 (SD = 1.3) for the FXS only matched subsample.

The scores of the subsamples on the theory of mind measure were also compared. Importantly, there was no difference between the subsample with autism and the FXS only matched subsample on the number of control questions answered correctly (near 42, or 70%, for each, $t(28) = -0.40, P = 0.69$, two-
researched, suggesting that they were similar in their ability to process the events depicted in the stories and the linguistic structure of the test questions. The number correct for the test questions was examined in a Subsample Diagnosis X Question Type (first- vs. second-order reasoning) ANOVA, with repeated measures on the last factor. Only the effect of Diagnostic group was significant, $F(1,28) = 4.96, P = 0.03$, partial $\eta^2 = 0.15$. The autism subsample performed significantly more poorly than the FXS only matched subsample. The mean number correct on the first-order test questions was 0.76 (SD = 0.77) and 0.33 (SD = 0.50) for the FXS only matched subsample and the subsample with autism, respectively. The mean number correct on the second-order test questions was 0.76 (SD = 0.70) and 0.11 (SD = 0.33) for the FXS only matched subsample and the subsample with autism, respectively. Note that one participant in the autism subsample was unable to complete this measure.

**Discussion**

The results provide an affirmative answer to our first question: Do youth with only FXS differ from those with co-morbid FXS and autism in the severity of their cognitive impairments? In particular, it was found that the youth with co-morbid FXS and autism were more likely to achieve the lowest possible standard score (i.e. 36) on the Stanford-Binet, 4th edition subtests than were the youth with FXS only. This finding is consistent with those of other studies of children (Bailey et al. 2001; Kau et al. 2004; Kaufmann et al. 2004; Philofsky et al. 2004), and with two other studies of adolescents and adults (Hagerman et al. 1986; Cohen 1995). Previous studies, however, were characterized by several methodological limitations that complicated interpretation of their results. These limitations were overcome in the present study by the use of the same non-verbal measure of intelligence and the same diagnostic procedures across participants, as well as by computation of an inferential test of the difference between the groups. Moreover, the number of participants with both FXS and autism has been small across studies, which suggested the need for replication with another sample. In summary, the present results, together with those of previous studies, demonstrate that cognitive impairments are more substantial in those with co-morbid FXS and autism than in those with only FXS, and that this difference is present at least from early childhood through young adulthood.

The results of the present study also provide an affirmative answer to our second question: Do youth with FXS differ from those with co-morbid FXS and autism in their profile of impairments in the domains of expressive language, receptive language and theory of mind? In particular, we found that youth with co-morbid FXS and autism are more impaired than those with only FXS in receptive language and theory of mind, but not in expressive language. Importantly, these differences held despite the fact that we controlled for cognitive level when answering this question, something that has not always been done in previous studies (e.g. Philofsky et al. 2004). These results are consistent with several previous studies in suggesting greater receptive than expressive deficits in those with co-morbid FXS and autism than in those with FXS alone (Bailey et al. 2001; Roberts et al. 2001; Kaufmann et al. 2004; Philofsky et al. 2004), and in suggesting that theory of mind is no more impaired (at least in terms of level of accuracy on false belief tasks) in those with only FXS than expected based on their levels of cognitive functioning (Garner et al. 1999; Abbeduto & Murphy 2004). The present study also demonstrates that this profile extends beyond childhood to adolescence and young adulthood.

The present study also demonstrates for the first time that the excessive impairments in receptive language that are characteristic of those with co-morbid FXS and autism are not limited to a single domain of language, but extend equally to the lexical, grammatical morphology and syntactic components of receptive language. Moreover, the present study is also the first to demonstrate that individuals with FXS who have autism perform more poorly on a false belief task designed to reflect core skills within a theory of mind than do FXS youth without autism at similar levels of cognitive development. Such findings suggest a profile similar to that seen in idiopathic autism, which is characterized by especially serious

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2 We also analysed the number correct on test questions (summed across first- and second-order questions) for only those participants answering five of six control questions correctly. This analysis yielded a significant difference between the subsamples with and without autism despite the greatly reduced sample size, $t(10) = 2.00$, $P = 0.037$ (one-tailed).

Taken together, these results suggest that the youth with co-morbid FXS and autism are not just more seriously delayed than are youth with FXS only; instead, the former are characterized by a profile of abilities that is different from that of the latter. The youth with co-morbid FXS and autism display an asynchronous profile in which receptive language and theory of mind skills are more seriously impaired than are expressive language and non-verbal cognition. In contrast, the youth with FXS only who are at similar cognitive levels display a ‘flat’, or synchronous, profile across these domains. Such results are consistent with the claim that those with co-morbid FXS and autism represent a distinct subtype of FXS as opposed to a variant of the syndrome that differs only in degree of impairment. The observed qualitative differences suggest that the combined effect of having both FXS and autism places the individual at a higher risk for problems with non-verbal cognition, language comprehension and theory of mind than does having FXS alone. In addition, the impact of having co-morbid FXS and autism appears not to be attenuated over time as the individuals move from early childhood into adolescence and young adulthood.

Although we did not include individuals with idiopathic autism in this study, the profile displayed by the youth with co-morbid FXS and autism is consistent with the profile previously reported for idiopathic autism (i.e. especially serious impairments in receptive language and theory of mind), as we noted previously. This pattern of results is not consistent with claims that autism in FXS is not ‘true’ autism (see Bailey et al. 2004 for a review). In this regard, it is interesting to note that recent evidence from neuroimaging studies suggests that the social impairment in idiopathic autism may have its origin in anxiety, as has been proposed for autism within FXS. In particular, Dalton et al. (2005) found that the youth with autism tended to avoid looking at the eyes in two-dimensional faces, but when they did, they showed greater activation of the amygdala than did controls. The amygdala typically is activated by stimuli that typically elicit negative emotions (e.g. fear), which suggests that social stimuli may elicit some form of social anxiety in individuals with idiopathic autism, just as has been proposed for individuals with co-morbid FXS and autism. Our findings suggest that the diagnosis of autism within FXS is also accompanied by the same profile of cognitive, linguistic and social-cognitive impairments as in non-FXS cases of autism.

The results of the present study are relevant to understanding the development of autism and ID in FXS. Cohen et al. (1991) described three possible pathways for the development of autism in FXS and its relationship to ID: (a) FXS leads to both ID and autism, with no causal relation between ID and autism; (b) FXS leads primarily to ID, with autism as a secondary sequela; and (c) FXS leads primarily to autism, with ID as a secondary sequela. The prevalence of ID exceeds the prevalence of autism in males with FXS, making the third scenario unlikely; but we could modify the third scenario to be a special case of the first scenario, i.e. FXS leads to ID, and in some cases also leads to autism, which can then, in those cases, lead to more substantial intellectual impairments than would be expected from FXS alone.

It is important to acknowledge several limitations of the present study. First, our findings concerning the profile of language and theory of mind impairments extend only to males. It would be interesting to see if females, who are less severely affected than males on average, also display the same profile of differences in relationship to autism status. Second, the small size of the FXS with autism group necessitates replication of these findings. Third, using the complete ADI-R and Autism Diagnostic Observation Schedule (ADOS; Lord et al. 1999) for diagnosis of autism would strengthen the present findings rather than relying on a screening instrument and clinical evaluation using less standardized methods as in the present study.

Future research that includes an idiopathic autism comparison group would be helpful for evaluating the impact of having co-morbid FXS and autism, and would contribute to solidifying the subtype associated with co-morbid FXS and autism. Such comparisons could be made at both the behavioural level, using measures such as those included in the present study, and measures derived from neuroimaging as in Dalton et al. (2005). A comparison group consisting of those with co-morbid FXS and PDD-NOS, a
diagnosis on the autism spectrum but falling short of the criteria for a diagnosis of autistic disorder, would also be a valuable addition. Would those with a diagnosis of co-morbid FXS and PDD-NOS be more similar to those with co-morbid FXS and autism, as would be expected if those with both FXS and autism represent a distinct subtype, or would they be more similar to those with only FXS? One of the challenges to making this comparison is being able to make a valid diagnosis of PDD-NOS. Lastly, it would be valuable to have a comparison group of typically developing participants, particularly for the false belief task, which does not have published norms.

In conclusion, it is worth noting that the co-morbidity of autism and various genetic syndromes presents a unique opportunity to explore biological mechanisms in the development of autism as well as developmental pathways in those with both autism and a genetic syndrome. Dykens et al. (1998) note that individuals with Prader–Willi syndrome resulting from a maternal disomy have an increased risk of autism compared with those with Prader–Willi syndrome resulting from a chromosome 15 deletion of paternal origin (Rogan et al. 1994). It also would be important to relate biological characteristics of FXS that can be quantified [e.g. per cent peripheral lymphocytes positive for fragile X mental retardation protein (FMRP), activation ratio] to the likelihood of an autism diagnosis. It would also be interesting to examine the behavioural profile of individuals with a diagnosis of both autism and other genetic syndromes, such as Down’s syndrome, to determine whether non-verbal cognition, receptive language and theory of mind are delayed in those with both autism and the genetic syndrome compared with those with only the genetic syndrome, as in our study, or whether there is another pattern of results in those with both autism and various other genetic syndromes. Relating the specific aspects of different skill profiles to biological markers in individuals with both autism and various genetic syndromes will help to illuminate the underlying biological mechanisms of these neurodevelopmental disorders.

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References


Appendix

Theory of Mind Tasks

SET-UP Place props & figures out in front of the participant and within examiner's easy reach. Props: miniature dinosaur, frog, tiger, bag of M&Ms candies, table with tablecloth, and cupboard.

INSTRUCTIONS

I’m going to tell you a story with these figures and this bag of M&Ms. I want you to listen and watch carefully because I’m going to ask you questions about things that happen in the story.

INTRODUCTION OF FIGURES

(Point to or hold the corresponding figure while saying:) This is Tiger. This is Dinosaur. This is Frog. and this bag of M&Ms belongs to Tiger. (Take away Dinosaur and Frog.)

(Note: When animals are not ‘in use’, they should be kept in the experimenter’s lap. Always point to or hold the figure being referenced, if that figure is on the table.)

STORY

One day, Tiger is in the kitchen. Tiger is eating some of her favorite candy, M&Ms. Tiger decides to go into the bedroom. First, Tiger puts the M&Ms under the table and then she goes into the bedroom.

Then Frog comes into the kitchen. Frog finds the M&Ms. Frog says, ‘Oh, that Tiger. She should not leave her M&Ms under the table.’ Frog takes the M&Ms and puts them in the cupboard.

OK [Participant’s name], I have some questions for you:

1st Order Critical Event

Did Tiger see Frog put the M&Ms in the cupboard?

If the participant responds incorrectly (i.e. says ‘yes’): correct him/her by saying:

Well actually the answer is ‘no, Tiger didn’t see Frog find the M&Ms.’

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Linguistic Control 1 (Place finger on frog.)
Does Frog know where the M&Ms are right now?

Linguistic Control 2 (Place finger on frog.)
Where would Frog look for the M&Ms right now?
Now, Dinosaur comes in. Dinosaur wants to ask you a question:

1st Order Ignorance (Hold Dinosaur while he speaks)
Hey [Participant’s name]: Does Tiger know where the M&Ms are right now?
Now, Dinosaur wants to ask you another question:

1st Order Belief (Hold Dinosaur while he speaks)
Hey [Participant’s name]: Where would Tiger look for the M&Ms right now?
Now, Frog and Dinosaur leave. Tiger comes back to the kitchen to get more M&Ms. Tiger looks under the table. The M&Ms aren’t there. So, Tiger looks in the cupboard and finds the M&Ms. Then Tiger puts the M&Ms back in the cupboard and leaves the kitchen.

2nd Order Critical Events (No figures out.)
Did Frog see Tiger find the M&Ms in the cupboard?
If the participant responds incorrectly (e.g. says ‘yes’):
correct him/her by saying:
Well actually the answer is ‘no, Frog didn’t see Tiger find the M&Ms’.
Frog and Dinosaur come back to the kitchen. Dinosaur wants to ask Frog a question:

2nd Order Ignorance (Hold dinosaur while he speaks)
Hey Frog: Does Tiger know where the M&Ms are right now? (Put down Dino and point to frog). What does Frog say to dinosaur?
Now, Dinosaur wants to ask Frog another question:

2nd Order Belief (Hold dinosaur while he speaks)
Hey Frog: Where would Tiger look for the M&Ms right now? (Put down Dino and point to frog). What does Frog say to dinosaur?
Now, I want to ask you two questions.

Reality Q (Leave out Frog and Dinosaur.)
Where are the M&Ms right now?

Memory Q (Leave out Frog and Dinosaur.)
Where did Tiger put the M&Ms at the very beginning of the story?
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