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Theory of mind deficits in children with fragile X syndrome

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Abstract

Background Given the consistent findings of theory of mind deficits in children with autism, it would be extremely beneficial to examine the profile of theory of mind abilities in other clinical groups such as fragile X syndrome (FXS) and Down syndrome (DS).
Aim The aim of the present study was to assess whether boys with FXS are impaired in simple social situations that require them to understand their own and others' mental states – in essence: do they have a 'theory of mind'?
Method Well-standardized tasks of theory of mind, the location change false belief task and the appearance–reality tasks were employed to examine whether any impairment might be specific to the FXS or part of a more generalized developmental deficit.
Results The results suggest that children with FXS do have impairment in theory of mind that is comparable to the deficit reported in other groups with learning disabilities such as DS. However, closer inspection of the impairment between these groups revealed qualitative differences in error types (realist vs. phenomenist), suggestive of atypical development that goes beyond general cognitive delay.
Conclusion The findings are discussed in terms of the teasing apart of different components of social cognition in order to identify syndrome-specific deficiencies and proficiencies.

Keywords autism, developmental psychopathology, Down syndrome, fragile X syndrome, social cognition, theory of mind

Introduction

Fragile X syndrome (FXS) is the world's most common form of hereditary intellectual disability (ID), with a prevalence of 1 in 4000 male births and 1 in 6000 female births and it is a result of silencing of a single gene, the fragile X mental retardation-1 (FMR1) gene (de Vries *et al.* 1997; Turner *et al.* 1996). In recent years, it has become one of the most widely researched and well-documented of genetic conditions. At a genetic level, it is now established that the FMR1 gene is the major contributor to the pathogenesis of FXS and that the key issues relate to a lack of messenger RNA (mRNA) and a lack or absence of the protein product of the

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FMR1 gene – FMRP. The extent to which these discoveries explain some of the phenotypic outcomes in FXS are beginning to be unravelled with the application of more finely tuned neuropsychological and neuropsychiatric approaches to understanding atypical development. In normal individuals there are 7–60 repeats with 30 repeats found on the most common allele (DNA sequence at FMR-1 gene site). Alleles with between 60–200 repeats are called premutations and generate some protein. When 200 or more CGG repeats are present, there is hypermethylation and a subsequent silencing of the FMR1 gene. This is commonly referred to as the FMR1 full mutation.

At a cognitive level, the syndrome presents with mild to severe ID, severe problems of inattention and hyperactivity (Turk 1998) and uneven abilities across and within cognitive domains. Relative strengths in language accompany relative weaknesses in visuospatial cognition (Freund & Reiss 1991; Cornish *et al.* 1999) and executive functioning, most notably for skills that require sequential processing, short-term memory recall, or reproduction of items in a serial or temporal order (Jakala *et al.* 1997; Wilding *et al.* 2002; Cornish *et al.* 2004a). In contrast, performance is relatively good on skills requiring simultaneous rather than sequential information processing, or on face and emotion recognition (Hodapp *et al.* 1991; Turk & Cornish 1998).

At the behavioural level, certain problems associated with FXS appear to reflect a link with autism. For example, children with FXS show some impairments in social and communicative functioning (Reiss & Freund 1990; Lachiewicz 1992; Turk & Cornish 1998), two of the three domains that comprise the triad of impairments that are central to the current diagnostic systems of autism (APA 1994). Within these domains, both groups display language delay, echolalia, and perseverative speech (Hagerman *et al.* 1986; Cohen *et al.* 1988; Hagerman *et al.* 1988), but commonalities between the groups also extend to attentional difficulties (Baumgardner *et al.* 1995; Turk 1998; Munir *et al.* 2000a), poor eye contact, and stereotypic movements (Cohen *et al.* 1988; Hagerman *et al.* 1988). The similarities between autism and FXS are consistent with evidence of the co-occurrence of the two disorders (Cohen *et al.* 1991; Feinstein & Reiss 1998; Bailey *et al.* 2001), because 2–4% of cases of autism appear to be caused by FXS (Fisch 1992; Bailey *et al.* 1996; Dykens & Volkmar 1997) and around 15–25% of children with FXS meet the diagnostic criteria for autism (Reiss & Freund 1990; Turk & Graham 1997; Dykens & Volkmar 1997; Bailey *et al.* 1998). Yet, despite these commonalities, certain social abilities that are particularly deficient among children with autism remain relatively intact in children with FXS, including recognition of emotion and face perception (Simon & Finucane 1996; Turk & Cornish 1998) and conversational abilities (Sudhalter 1996). So while similarities between syndromes are present, the differences in behavioural characteristics necessitate the development of cognitive and behavioural profiles of intact and impaired abilities in FXS that will facilitate comparisons between related disorders.

One way to test the association between FXS and autism would be to assess 'theory of mind' among children with FXS because the deficit in 'theory of mind' appears to underlie many of the social and communicative impairments that are characteristic of autism (for a review see Yirmiya *et al.* 1998). Much of the research about 'theory of mind' ability relies on false belief (FB) tasks as indicators of whether or not a child has mental state understanding. Children with autism show pronounced deficits in mental state understanding or the commonly used FB tasks, in which one's understanding of the event or situation must be differentiated from others, or appearance–reality (AR) tasks, in which one must distinguish between the perception of an object (its appearance) and their knowledge of it (its real identity) (Baron-Cohen 1989). On the AR tasks, children with autism make significantly more overall errors than children with Down syndrome (DS). More specifically, children with autism make qualitatively different types of errors (phenomenist) compared with children with DS who make an equal number of phenomenist and realist errors (see *Method* section for examples of these error types).

Given the consistent findings of theory of mind deficits in children with autism, it would be extremely beneficial to examine the profile of theory of mind abilities in other clinical groups such as FXS. Of the few published studies on theory of mind abilities in other syndromes, an initial study by Garner *et al.* (1999) reported that more children with FXS failed standard FB tasks than a comparison group of children with ID of unknown aetiology. In the present

study, we extend these findings in two main ways. Firstly, we incorporate a relatively large sample size of children with FXS. Secondly, by comparing performance across two distinct syndromes of known aetiology we begin to delineate the specificity of theory of mind deficits across neurodevelopment disorders.

Our objectives were to determine whether young males with FXS, who were screened for autism and did not receive a diagnosis, would display a specific deficit in theory of mind as measured by both FB (i.e. Sally Anne) and AR tasks, on which the typically developing trajectory is well-documented (Frith & Frith 2003). Male children with DS (Trisomy 21) matched for chronological and verbal mental age were included as the comparison group because FXS and DS represent the two most common causes of ID for which aetiology is known but who often display contrasting patterns of neurodevelopmental proficiencies and deficiencies (Hodapp *et al.* 1992; Burack *et al.* 1999; Wilding & Cornish 2004). However, given the behavioural similarities between autism and FXS, we expected that the performance on theory of mind tasks by children with FXS would reflect a similar pattern of impairment as those seen among children with autism.

Subjects and method

Sample

The present study involved two groups of participants: (1) 28 boys with FXS (mean chronological age 11 years and 2 months; range 7–15 years) recruited from the UK parent support group. Diagnosis of FXS was established by DNA testing which confirmed the presence of FMR-1 full mutation, and (2) 26 boys with DS (mean chronological age 11 years and 11 months; range = 7.5–15.10, SD = 32 months) recruited from a UK parent support group. Diagnosis of DS had previously been established by cytogenetic testing which confirmed a karyotype with a free trisomy 21. Both syndrome groups were part of an extensive neuropsychological study that assessed performance across a range of cognitive domains (e.g. Munir *et al.* 2000a,b; Wilding *et al.* 2002; Cornish *et al.* 2004b).

All boys with FXS and DS were receiving special education and none were living in institutional settings. None of the children met the ICD-10 criteria for autism. Furthermore, none of the children in any of the groups had sensory impairments including hearing deficits and decreased visual acuity. Finally, none of the children were on stimulant drugs such as methylphenidate (Ritalin) for hyperactivity which might influence cognitive performance.

Verbal mental age (VMA) was assessed using the British picture vocabulary scale (BPVS) (Dunn *et al.* 1982). The VMA for the FXS group was 6 years and 11 months (range = 4.1–10.9, SD = 21 months). For the DS group, the VMA was 6 years and 7 months (range = 4.8–9.9, SD = 15 months).

Data collection and measures

The location change false belief task

The procedure for the location change FB task was consistent with that utilized by Baron-Cohen *et al.* 1985). Each child was introduced to two doll protagonists, Sally and Anne. Sally placed a marble into a basket and then left the scene. Anne then transferred the marble from the basket to the box and left the scene. At the time Sally returned, the experimenter asked the child a series of questions, 'Where will Sally look for her marble?', the reality question 'Where is the marble really?', and the memory question 'Where was the marble in the beginning?'. This task was then repeated using a new location for the marble, so that now there were three locations that the participant could point to (i.e. box, basket and experimenter's pocket). On both trials of the task, a child scored one point for the belief question if they pointed to the location at which Sally had originally left the marble.

The appearance–reality tasks

The procedure for the AR tasks was consistent with that employed by Baron-Cohen (1989). After a warm-up procedure, each child was also administered a memory pretest in which an orange filter was placed over a white piece of paper, thus changing it's apparent colour. The child was then asked, 'When I take this away, will the paper look white or orange?' This pretest indicated that the child was able to remember an object's original colour and understand that a filter did not permanently alter the colour of an object. In order to ensure that all participants would understand the AR tasks, only those who

passed this pretest were administered the experimental tasks.

Following the pretest, four AR tasks, with two trials each, were presented in random order. These tasks consisted of the separate manipulation of an object's colour, size, material, and identity. In each trial, an appearance and a reality question was asked and once the child had answered both questions, their responses were coded into correct, phenomenist, realist or other. So, for example, on the first of two colour trials, a bottle of milk was shown to the child, who was asked to name the object and its colour. An orange filter was then placed in front of the object and the child was asked the appearance question 'Now what colour does the milk look?' and the reality question 'What colour is it really?' A correct response was that the milk looked orange but was really white, a phenomenist response was that the milk looked orange and really was orange, and a realist response was that the milk looked white and really was white. A piece of white chalk was used for the second colour trial. A similar procedure was followed for the remaining AR tasks: size, material and identity.

A correct answer to a pair of AR questions was awarded 1 point. Each child could therefore score a maximum of 8 points (1 point per trial, 2 on each of the four tasks). If three or more tasks (i.e. colour, size, material, identity) were passed, this was recorded as a pass on the AR distinction overall.

Results

The false belief task

The number of children by syndrome group who passed both the control memory and the FB test questions are presented in Table 1. For Trial 1, 13 children from the FXS group and 12 from the DS group passed the false belief, memory, and reality questions. For Trial 2, 12 children from FXS group and 12 from the DS group passed the false belief, memory and reality questions. There were no significant differences between these two groups on the belief questions on either Trial 1 or 2 (Trial 1: Chi-square = 0.080, d.f. = 1, $P = 0.77$; Trial 2: Chi-square = 0.00, d.f. = 1, $P = 0.98$). For Trial 1, of those children who passed the control memory but failed the belief task, 10 were FXS and 5 were DS. However, for Trial 2, 6 of the 10 children with FXS failed the control memory questions, as presented in Table 1.

The appearance–reality tasks

Overall, the pass rates on the AR tasks were similar for the two syndrome groups, with 19 children with FXS passing three or more tasks as compared with 18 of children with DS. No significant differences were found between these groups on the AR distinction (Chi-square = 0.01, d.f. = 1, $P = 0.91$).

A task-by-task analysis (summarized in Table 2) revealed similar performances by both groups on tasks of colour (Chi-square = 2.23, d.f. = 2, $P = 0.135$), size (Chi-square = 2.42, d.f. = 2, $P = 0.298$), and material (Chi-square = 0.403, d.f. = 2, $P = 0.818$). All three of these tasks had a pass rate of over 75% across both groups. The colour task resulted in the highest success rate ($n = 54$; 96.3%) and the task producing the greatest difficulty, for both the FXS and the DS groups, was the identity task ($n = 28$; 52%). Closer inspection of performance on the identity task, revealed that of the FXS group who

Table 1 Performance of the children with fragile X syndrome (FXS) and Down syndrome (DS) on the false belief (FB) task test and memory questions for Trials 1 and 2

	FXS ($n = 28$)		DS ($n = 26$)	
Performance	**Trial 1**	**Trial 2**	**Trial 1**	**Trial 2**
Passed FB, passed memory + reality	13 (46.4%)	12 (42.9%)	12 (46.2%)	12 (46.2%)
Passed FB, failed memory + reality	1 (4.6%)	1 (4.6%)	0 (0%)	0 (0%)
Failed FB, passed memory + reality	10 (35.7%)	4 (14.3%)	5 (19.2%)	3 (11.5%)
Failed FB, failed memory + reality	4 (14.3%)	11 (39.3%)	9 (35.6%)	11 (42.3%)

Table 2 Frequency of errors across the four appearance–reality distinction tasks

Object's Dimension	Errors	FXS	DS
Colour	Phenomenist	0	0
	Realist	0	2
Size	Phenomenist	2	0
	Realist	4	6
Material	Phenomenist	4	3
	Realist	2	1
Identity	Phenomenist	3	11
	Realist	11	3

FXS, fragile X syndrome; DS, Down syndrome.

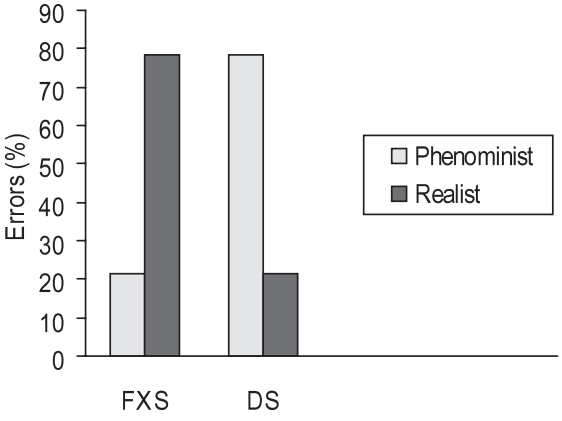

Figure 1 Percentage of realist and phenomenist errors made by the FXS and Down syndrome (DS) groups on the appearance–reality (AR) identity task.

made errors, 78.6% ($n = 11$) of their total errors were realist while only 21.4% ($n = 3$) of the total errors committed by the DS group were realist. This syndrome-specific difference was highly significant (Chi-square = 9.23, d.f. = 2, $P = 0.01$). See Fig. 1.

Discussion

A primary aim of the present study was to examine performance on well-standardized tasks of theory of mind, the location change FB task (Baron-Cohen *et al.* 1985) and AR tasks (Baron-Cohen 1989), among boys with FXS as compared with a group of boys with DS. In the FB task, approximately half of the FXS boys performed the task successfully by accurately answering the critical question of 'Where will Sally look?' after she returns. This success rate was similar to that of boys with DS and consistent with previous reports of a 50% accuracy rate on the FB task in children with DS compared with only a reported one-third of children with autism (Yirmiya *et al.* 1996). Taken together, these findings provide additional evidence for possible qualitative differences between the phenotypic outcomes of children with FXS and autism. However, this interpretation needs to be treated with some degree of caution as a result of the absence, in the present study, of a comparison group of children with autism.

Consistent with findings on the FB task, the performance of children with FXS and DS, on the AR tasks, differed from the performance previously reported in children with autism who consistently failed to make appearance–reality distinctions (Baron-Cohen 1989). Overall, more than two-thirds of the FXS and DS groups passed three or more tasks indicating that the ability to understand their own mental states was relatively unimpaired in these syndrome groups. However, when errors occurred they were committed predominantly on the identity task with both groups making over 50% of errors. Upon closer inspection of these error types, an interesting profile of differences between the FXS and DS groups emerged. Compared with children with DS who made predominantly phenomenist errors (78% vs. 21%) on this task, children with FXS made predominantly realist errors (78% vs. 21%)

This tendency, of the DS group, towards phenomenist errors has also been previously reported among children with autism (Baron-Cohen 1989) and perhaps indicates a commonality between these syndrome groups. The tendency towards realist errors among children with FXS, however, is a novel finding and suggests that, in contrast to children with DS and children with autism, the FXS child demonstrates an inability to dissociate appearance from reality, that is, they ignore the appearance of an object and instead rely solely on real knowledge. In contrast, phenomenist errors suggest that the perceptual information of an object, even if it contradicts the child's real knowledge of that object, overrides all other representations. So, in the present study, children with DS display an inability to dissociate reality from appearance, but contrary to children with FXS, they ignored

their real knowledge about an object and relied instead on the changed appearance of the object. This cross syndrome dissociation in error types underlines the importance of looking beyond global outcomes of cognitive and behaviour functioning and to move towards isolating those subtle differences in information processing that point to syndrome-specific atypical developmental trajectories.

In summary, the findings from the present study add to the emerging profile of social cognitive deficits in children with FXS. They are important for two main reasons. Firstly, we provide evidence that children with FXS experience theory of mind difficulties in their ability to understand the belief and intentions of others (as represented by the FB task) at a level comparable to children with DS. These findings extend those of Garner *et al*. (1999) and also support previous efforts to examine deficits in relation to levels of performance reported among atypically developing children outside of autism (Yirmiya *et al*. 1996). However, the extent of the deficit in FXS is clearly not as severe as that previously reported in children with autism suggesting a qualitative difference between the two conditions. Secondly, although the FXS and DS groups appeared comparable in their ability to make AR distinctions (at a much greater level of success than that reported in autism), upon closer inspection of our data, important differences in error types revealed subtle processing deficits between the two syndrome groups. Therefore, it is possible that developmental outcomes, even when behaviourally equivalent, may differ across syndromes and among typically developing children.

Finally, it is also important to recognize that theory of mind is just one aspect of social cognition. Other components such as emotion and face recognition, eye gaze, social anxiety, and perception are also important aspects of social and communicative functioning that need to be explored in further detail. Moreover, a cross syndrome comparison design that incorporates a longitudinal component would further facilitate the teasing apart of important differences and commonalities. This would be an important step forward towards the development of precise profiles of syndrome-specific cognitive abilities and atypical developmental pathways. These profiles would serve a clinical and educational purpose by aiding in the design of remedial programs that address the varying proficiencies and deficiencies unique to particular syndrome groups.

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