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## Imitation in fragile X syndrome: Implications for Autism

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## Imitation in fragile X syndrome:

### Implications for autism

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### Abstract

To address the specific impairment of imitation in autism, the imitation abilities of 22 children with fragile X syndrome (FXS) with and without autism were compared. Based on previous research, we predicted that children with FXS and autism would have significantly more difficulty with non-meaningful imitation tasks. After controlling for full-scale IQ and age, the groups did not differ in their overall imitation accuracy scores, but analysis of error patterns revealed that children with FXS and autism made more groping errors and additional movements than the comparison group. These error patterns are consistent with the hypothesis that an action production system deficit plays an important role in the overall imitation deficit in autism, at least in children with FXS.

### Keywords

autism; fragile X syndrome; imitation

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Fragile X syndrome (FXS) is the most common inherited cause of mental retardation as well as the most common identifiable single gene mutation associated with autism (Hagerman, 2006). It occurs in approximately 1 in 3600 males and 1 in 6000 females. The syndrome generally results from the transcriptional silencing of the fragile X mental retardation gene

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(FMR1) and consequent absence of the FMR1 protein. The behavioral phenotype includes cognitive and language problems, attention deficit and hyper-activity, social anxiety, avoidance of eye contact, hand stereotypies and autism, which is more prevalent than in the general population. The prevalence rate of autism in individuals with the syndrome is estimated to be 25–35 percent, making this singular genetic syndrome a good model for the study of possible causal mechanisms of autistic development. One way of studying the proposed overlapping behavioral, neural and genetic mechanisms in FXS and autism (Belmonte and Bourgeron, 2006) is to identify common behavioral phenotypes and their underlying molecular and cognitive predictors (Loesch et al., 2007; Nowicki et al., 2007).

From the late 1980s onward, autism has been conceptualized mainly as a disorder involving social impairment. The proposal that difficulties in imitating others could be a significant contributor to the social deficits in autism was put forward even before that period (DeMyer et al., 1972), but systematically for the first time in a paper by Rogers and Pennington (1991). Since the ability to imitate is present from the neonatal period onwards (Meltzoff and Moore, 1977), it can be seen as one of the earliest signs of emerging social relationships and communication. It influences the development of intersubjective relatedness, self–other representations, language and communication, and the theory of mind (Decety and Chaminade, 2003; Meltzoff, 2002; Rogers, 2006; Williams et al., 2004).

Over the past 20 years, considerable evidence for imitation deficits in individuals with autism of all ages has emerged. These deficits are seen across a range of tasks including gestural imitation, facial imitation, and imitation of actions performed with objects (Rogers and Bennetto, 2000; Rogers et al., 1996; Williams et al., 2004). However, it seems that children with autism have more difficulties with meaningless gestures than with familiar, meaningful actions or actions with objects (Rogers et al., 1996). This may suggest that a perceptual-motor impairment, rather than a cognitive weakness of symbolic representation, causes imitation problems in autism.

Recently Vanvuchelen et al. (2007a) showed that perceptual-motor components may have a key role in imitation difficulties in autism. They compared the performance of groups of boys with mental retardation, low-functioning autism, high-functioning autism and typically developing boys on an imitation test (meaningful and non-meaningful gestures) and standardized general motor tests. The authors found that all boys with autism had more difficulties imitating non-meaningful compared to meaningful gestures. In addition to impaired imitation abilities they also noticed poorer general motor performance in boys with autism compared to the other groups included in the study.

In their following study Vanvuchelen et al. (2007b) investigated the underlying mechanisms of imitation problems in boys with autism by using a scoring system based on four different error types: content, spatial, temporal and behavioral errors. They considered spatial and temporal errors as being typical of problems in the action production system and content errors as being typical of difficulties in the action conceptual system (Rogers, 1999; Rothi et al., 1997). The results revealed that, in groups with autism, imitation required far more effort (more attempts) and was less precise (spatial errors) than in comparison groups of children with learning disabilities and typically developing children, thus supporting the assumption

that the underlying mechanisms are linked to a greater extent to the action production system.

Imitation abilities in children with FXS have been previously investigated in a study by Rogers et al. (2003). They compared the imitation performance of toddlers with autism and toddlers with other developmental disorders including FXS. Because of the small proportion of toddlers with autism in the group of toddlers with FXS, the comparison between the two subgroups of FXS children with and without autism was informative only in an exploratory context. The results of the study showed that children with FXS and autism performed similarly to the idiopathic autism group on imitation tasks, while the performance of children with FXS without autism more closely resembled the performance of the group with other developmental disorders.

In the present study we used the model of FXS to investigate more systematically the possible underlying mechanisms of imitation difficulties in autism. Considering that children with FXS with and without autism have many problems in different domains relating to the genetic disorder, we aimed to find out if these two groups differed in their imitation of non-meaningful gestures. By using an Imitation Battery that assessed both the accuracy of imitation and the error types committed, we wanted to look at imitation difficulties stemming from the action conceptual and action production systems separately. Finally, we also investigated the action production system in terms of perceptual-motor abilities using the Developmental Test of Visual-Motor Integration.

## Methods

### Participants

Twenty-eight children with FXS, aged 5 to 14 years, participated in the study. All children had clinical evaluation including a neurological examination. They did not have any visual, hearing or severe motor impairment that could contribute to their imitation abilities. All but one were right handed. The diagnosis of FXS was based on molecular genetic testing.

The included children were divided into two groups. The first group (FXS + autism) consisted of 17 children who met criteria for autism or ASD on at least two out of the three following diagnostic systems: DSM-IV, ADOS and ADI-R. The comparison group (FXS) consisted of 11 children without autism or ASD as obtained by the previously mentioned criteria. The full-scale IQ standard scores were obtained from the WISC-R or the Wechsler Abbreviated Intelligence Scale and the Kauffman Assessment Battery for Children mental processing composite and the Vineland Scales of Adaptive Behavior adaptive behavior composite (two children). If the score on the Vineland composite was lower than 40, then this score was used for analyzing the full-scale IQ.

To control intervening variables we then paired each child in the FXS group with one in the FXS + autism group matched for full-scale IQ and age. Therefore each final study group had 11 participants (Table 1). Children included in the final study groups were all assessed based on DSM-IV criteria and had all completed the ADOS. ADI-R assessment was done in seven children in the FXS + autism group and four children in the FXS group. In the FXS + autism

group, all children met DSM-IV diagnostic criteria. On the ADOS three children reached cutoff criteria for ASD and eight others for autism, while on the ADI-R six out of seven children scored above the diagnostic threshold. The FXS + autism group consisted of eight boys and three girls. All children in the FXS comparison group scored below the diagnostic threshold for ASD on the ADOS. Among them one child met DSM-IV criteria and two others scored above the cutoff criteria on the ADI-R. The FXS group included one girl and 10 boys.

## Measures

**Symptoms of autism**—The Autism Diagnostic Interview–Revised (ADI-R: Lord et al., 1994) is a structured, semi-standardized parent interview developed to assess the presence and severity of symptoms of autism in the three main domains involved in autism: social relatedness, communication and repetitive, restrictive behaviors. The child is classified as having autism if he or she meets the cutoff criteria in all three areas.

The Autism Diagnostic Observation Schedule (ADOS: Lord et al., 1999) is a semi-structured standardized observation method using developmentally appropriate social and toy-based interactions to elicit symptoms of autism in four areas: social interaction, communication, play and repetitive behaviors. The ADOS diagnostic algorithm allows for the classification of children as having autism or ASD based on selected items on the communication and social subscales. The ADOS is intended to be one source of information used in making a diagnosis of autism/ASD, but is not sufficient to establish a diagnosis on its own.

**Visual-motor assessment**—The Developmental Test of Visual-Motor Integration (VMI: Beery, 1997) was performed. The copy test measures motor and perceptual skill integration. The visual perceptual supplemental test measures perceptual skills without a motor component. During the supplemental test the child is asked to match shapes from increasingly complex sets by pointing to the correct response. The motor coordination supplemental test measures precise motor coordination within a targeted area. The child is asked to draw within a predefined area by connecting dots of increasingly complex shapes.

**Imitation battery**—Four kinds of meaningless tasks were performed: single face, single hand, complex hand and movement sequences (Rogers et al., 2005). Two types of code were used to score performance: the accuracy code and the error code. The accuracy code was used for those aspects that were different for each class of movement:

1. The single face movements consisted of eight tasks: bilateral lip retraction, upper teeth on lower lip, raised eyebrows, puckered lips, tongue protrusion on side, tongue swipes lip, wrinkle nose and wink eye. Each item was scored according to two aspects, e.g. for bilateral lip retraction (lip retracted and teeth exposed), a correct imitation for each of the two aspects scored 1, while an incorrect imitation scored 0, giving a total score range of 0–16.

2. The single hand movements consisted of six tasks according to ASL: E, K, A, F, X and 'I love you'. Each item was scored according to finger position and orientation as 1 or 0. Total scores ranged from 0 to 12.
3. Items on the complex hand movement were performed with both hands and consisted of five tasks: little fingers, thumbs touching, knuckles out; interlocking fingers; thumb triangle pointing up; inverted index and little finger; palms up, thumbs touching and pointing out. Each item was scored 1 or 0 according to the hand position, finger position and orientation, with a total score range of 0–15.
4. The movement sequences consisted of six tasks: hand on lap; arm across chest; hand from shoulder to front; hand slaps arm; arm flexes at elbow; hand moves across forehead. Each item was scored according to the start position, plane of movement, posture change, and end position. Correct start and end imitation positions scored 2, partially correct 1 and inaccurate 0. For movement and posture change there were two possibilities, 1 or 0. The scores ranged from 0 to 36.

A total imitation scale was defined as the sum of all items included in the single face, single hand, complex hand and movement sequences imitation scales.

The following errors were coded if present: groping for additional movements that helped to improve the imitation; extraneous movement for additional movement that added to the target, e.g. overflow movements; bilateral error for movements produced by two hands instead of one; and mirror errors for performing the act as if looking into a mirror. The total number of errors per class of movement was included in the analysis.

The tasks were performed in one session lasting 15 to 30 minutes. During the imitation tasks the child sat in front of the person modeling the task. After the task was modeled, the child was asked to imitate the task as accurately as possible. The performance was recorded and later coded. Any item that could not be scored due to lighting or an inappropriate camera angle was marked as 'not scored'. All scores were initially obtained by one rater who was partially blind to group membership; so another rater, blind to group membership, scored five subjects (23%) to obtain reliability. Inter-rater reliability was calculated using interclass correlation coefficient. It ranged from 0.88 to 0.99 for the imitation score as a whole and all four imitation subtests, and from 0.80 to 0.92 for errors.

### Statistical analysis

Before we conducted statistical analyses, missing data for imitation test items were substituted using the median values of the appropriate group for that test item. The missing values resulted from items not being scored due to technical difficulties (camera angle, poor lighting). Missing values were present in seven children in the FXS group and three children in the FXS + autism group. Only one child in the FXS group had data lacking for more than two out of 25 items; the remaining children had missing data on either one or two test items. The missing data were distributed unevenly between both groups. In the FXS + autism group, missing values constituted 1.5 percent of the group's data; while in the FXS group,

missing values represented 6.8 percent of the group's data, a difference that was significant ( $\chi^2 = 7.47, p = 0.006$ ). In order to ensure that substitution of missing values did not distort the results, we conducted the statistical analyses with and without data substitution using the SPSS 13.0 statistical software package (Apache Software Foundation, 2004).

The Imitation Battery (Rogers et al., 2005) is a new instrument; hence we first analyzed the reliability of the scales used. Cronbach  $\alpha$  coefficients were used to assess the internal consistency of the items included in the single face, single hand, complex hand and movement sequences scales as well as the total imitation scale.

Group differences in age, IQ and VMI scores were then analyzed using one-way analysis of variance (ANOVA). Afterwards, two multiple analyses of covariance (MANCOVAs) were used to compare both groups on the imitation scales. One MANCOVA was used to look at imitation accuracy scores, another to examine potential differences on imitation error scores. Age and full-scale IQ were included in the analyses as covariates. The MANCOVAs were followed up by ANOVAs looking at the effect of group membership on individual imitation accuracy and imitation error scales. Effect sizes were estimated using partial  $\eta^2$ . According to the recommendations of Kirk (1996),  $\eta^2$  effect sizes around 0.01 were considered small, those around 0.06 medium and those around 0.14 large. We tested only for first-order effects due to the restricted sample size. Using Pearson partial correlation coefficients, we also attempted to evaluate the associated visuomotor skills and various imitation scales after controlling for age and full-scale IQ.

## Results

The distribution of scores on the independent variables was normal (Kolmogorov–Smirnov test  $p$ -values between 0.239 and 0.980), with the exception of verbal IQ (Kolmogorov–Smirnov  $Z = 1.40, p < 0.04$ ). As verbal IQ scores were positively skewed ( $s_k = 1.216, SE_{s_k} = 0.512$ ), further analysis of group differences on verbal IQ was done using the non-parametric Mann–Whitney  $U$ -test.

### Age and intelligence

The groups did not differ significantly in terms of age, performance IQ and full-scale IQ (Table 1). The groups were also matched in terms of verbal IQ (Mann–Whitney  $U = 36.0, p = 0.28$ ). The average verbal IQ in the FXS + autism group was 51.5 (SD = 8.1, range = 40–64) and 58.6 (SD = 14.7, range = 46–86) in the FXS group.

### Imitation: reliability analyses

The reliability of single face, single hand, complex hand and movement sequences imitation scales, as assessed by internal consistency, was found to be satisfactory. Internal consistency  $\alpha$  coefficients ranged from 0.62 for the complex hand scale to 0.77 for the single face scale. The  $\alpha$  coefficient for the total imitation scale also indicated adequate reliability ( $\alpha = 0.83$ ).



### Imitation: group differences

A MANCOVA was conducted to investigate differences between the two groups on imitation accuracy scales. Levene's tests indicated the error variances of the dependent variables to be equal between the groups,  $p$  ranging from 0.06 to 0.89. MANCOVA results did not show a significant main effect of group membership (Wilks's  $\Lambda = 0.79$ ,  $F(4, 15) = 1.02$ ,  $p < 0.431$ ,  $\eta^2 = 0.213$ ), age (Wilks's  $\Lambda = 0.80$ ,  $F(4, 15) = 0.96$ ,  $p < 0.457$ ,  $\eta^2 = 0.204$ ), or full-scale IQ (Wilks's  $\Lambda = 0.73$ ,  $F(4, 15) = 1.42$ ,  $p < 0.276$ ,  $\eta^2 = 0.274$ ). Repeating the analysis using list-wise deletion of cases with missing values did not change the results significantly. Neither group membership (Wilks's  $\Lambda = 0.45$ ,  $F(4, 5) = 1.53$ ,  $p < 0.321$ ,  $\eta^2 = 0.551$ ), nor age (Wilks's  $\Lambda = 0.51$ ,  $F(4, 5) = 1.20$ ,  $p < 0.414$ ,  $\eta^2 = 0.489$ ), nor IQ (Wilks's  $\Lambda = 0.37$ ,  $F(4, 5) = 2.12$ ,  $p < 0.215$ ,  $\eta^2 = 0.629$ ) had a significant effect.

A second MANCOVA was conducted to examine group differences on the imitation error scales. The results showed a significant multivariate effect of group membership on imitation error scores (Wilks's  $\Lambda = 0.45$ ,  $F(5, 12) = 2.99$ ,  $p < 0.056$ ,  $\eta^2 = 0.555$ ). Neither age (Wilks's  $\Lambda = 0.55$ ,  $F(5, 12) = 1.99$ ,  $p < 0.153$ ,  $\eta^2 = 0.453$ ) nor full-scale IQ (Wilks's  $\Lambda = 0.67$ ,  $F(5, 12) = 1.21$ ,  $p < 0.363$ ,  $\eta^2 = 0.335$ ) had a significant effect on imitation error scores. As was the case on the imitation accuracy scales, Levene's test showed no differences in error variance between groups on imitation error scales,  $p$  ranging from 0.29 to 0.93.

As seen in Table 2, univariate analysis revealed no group differences in imitation accuracy scores. There were, however, significant and large group differences in the number of two error types. Children in the FXS + autism group committed more groping and extraneous movement errors.

### Imitation: visuomotor abilities

After statistically controlling for age and full-scale IQ, the single hand imitation scores correlated significantly with the results obtained by the copy test ( $r = 0.642$ , d.f. = 14,  $p < 0.007$ ) and visual perceptual subtest ( $r = 0.507$ , d.f. = 14,  $p < 0.045$ ). Children with lower motor scale scores tended to commit more groping errors ( $r = -0.467$ , d.f. = 14,  $p < 0.079$ ), more extraneous movement ( $r = -0.451$ , d.f. = 14,  $p < 0.092$ ) and more mirroring errors ( $r = -0.533$ , d.f. = 14,  $p < 0.041$ ).

## Discussion

By assessing imitation abilities in children with FXS, we used this singular genetic disorder as a model to understand the relationship between imitation and autism. The Imitation Battery included in our study enabled us to separately assess the accuracy of imitation and errors committed. Using MANCOVA, no differences were found in the accuracy of imitation between the two groups. However, significantly more groping errors and additional movements were found in the children with both FXS and autism.

In a previous study, Rogers et al. (2003) examined the imitation abilities of toddlers with FXS with and without autism. Both imitation measures (manual imitation, oral-facial imitation and imitation of actions on objects) and tests of motor performance were included

in order to examine the possible underlying mechanisms of imitation abilities. Compared to children with developmental delay (including those with FXS without autism), children with autism (including those with FXS) performed more poorly on two out of three imitation subscales. However, no significant group differences were found in fine motor functioning, gross motor functioning and praxis using non-standardized motor and praxis tests. The authors concluded that the study did not yield evidence supporting an autism-specific deficit in motor coordination or a generalized motor planning or motor execution deficit.

In contrast, several other studies have reported a greater prevalence of motor deficits in children with ASD compared to children with developmental delay or typically developing children. These deficits included clumsiness, motor non-coordination, disturbances in reach-to-grasp movement, deficits in gross and fine motor movement and impaired postural control (Ming et al., 2007; see Rogers, 1999 for review).

Studies assessing both imitation and motor abilities are, however, rare. In one such study, Vanvuchelen et al. (2007a) showed that boys with low-functioning autism as well as those with high-functioning autism performed significantly worse than boys with mental retardation or typically developing children on standardized motor tests as well as imitation tasks requiring the imitation of non-meaningful gestures. In contrast, only boys with low-functioning autism performed worse in imitation of meaningful gestures. The fact that children with autism have more difficulties with non-meaningful gestures compared to familiar, meaningful actions or actions with objects has previously also been demonstrated by other studies (Rogers et al., 1996). This line of evidence implicates a perceptual-motor impairment, rather than a cognitive weakness of symbolic representation, as a cause of imitation problems in autism.

Our findings that children with lower scores on the motor coordination supplemental test of the VMI test tended to commit more groping errors, more extraneous movement and more mirroring errors suggest a relationship between these kinds of errors and fine motor difficulties. The finding that single hand imitation scores correlated significantly with the results obtained by the copy test and visual perceptual subtest also implicate a perceptual-motor aspect of imitation difficulties.

When one is studying the motor mechanism involved in the imitation deficits in autism, a neuropsychological approach, which distinguishes between an action production system and an action conceptual system, can be useful (Rothi et al., 1997). In contrast to the majority of previous studies on imitation, our Imitation Battery included both accuracy and error codes, allowing us to examine these two different systems separately. Our finding that both groups of children differed not in the accuracy of imitation, but rather in the number of errors committed, supports the results of Vanvuchelen et al. (2007b) who showed that children with autism needed more attempts to imitate, made more synkinesias (spatial errors) and displayed a greater amplitude in their gestures compared to control groups. The 'need for more attempts' in the study by Vanvuchelen et al. was similar to our concept of 'groping' errors, while spatial errors ('amplitude error') represented an error type comparable to our own 'extraneous movements' errors. As spatial errors and a 'need for more attempts' are due to difficulties in planning and executing responses, our results support the assumption that

the underlying mechanism in the overall imitation deficit in autism is to a greater extent linked to an impairment of the action production system rather than the action conceptual system.

The groping errors and additional movements, reflecting impairment in the action production system, might also point toward greater problems with balance, precise motor coordination and timing. Coordinated and well timed movements require the normal operation of a number of different brain structures, including the basal ganglia and cerebellum, which have been proposed to play a vital role in motor timing and error prediction (Dreher and Grafman, 2002). Neuroanatomic studies, magnetic resonance imaging and magnetic resonance spectroscopy studies have shown the cerebellum to be impaired in individuals with autism (Bauman and Kemper, 2005; Hardan et al., 2001; Otsuka et al., 1999). Since the cerebellum is also impaired in FXS (Gothelf et al., 2008; Huber, 2006; Kaufmann et al., 2003), children with FXS and autism may experience an additive effect of cerebellar pathology.

The conclusions of our study must be tempered by its limitations. One of the main drawbacks of the study was the small sample size of the groups which was due to the specific target group. In addition, using a standardized motor test to assess fine and gross motor abilities in combination with an Imitation Battery would have provided clearer evidence of a relationship between imitation and motor skills in children with FXS with or without autism. A replication of the study with the inclusion of standardized motor tests would therefore be very helpful.

## Conclusions

The fact that autism is much more prevalent in FXS compared to the general population makes this singular genetic syndrome a good model for studying possible causal mechanisms of autistic development. One of the first steps that can clarify the complex relationship between FXS and autism is to identify possible overlapping behavioral phenotypes. The present study is the first to systematically address imitation abilities in FXS, taking into account its comorbidity with autism. The results indicate that children with FXS and autism experience greater impairment in the action production aspect of imitation than those with FXS alone. Our findings also indicate an important role of the action production system in the overall imitation deficit in autism, at least in children with FXS.

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**Table 1**

Participant characteristics

	<i>FXS + autism</i>		<i>F</i>	<i>p</i>	$\eta^2$
	<i>Mean (SD)</i>	<i>Range</i>			
Chronological age	9.8 (2.6)	5–13	10.0 (2.7)	6–14	0.03 0.87 0.001
Full-scale IQ	52.7 (16.7)	40–96	56.5 (12.7)	42–80	0.35 0.56 0.017
Performance IQ	53.5 (9.7)	46–77	58.7 (11.0)	46–75	1.25 0.28 0.065
VMI total score	58.4 (14.4)	45–88	60.5 (9.1)	45–76	0.14 0.71 0.008
VMI visual perceptual test	63.0 (20.6)	45–109	66.1 (14.3)	54–102	0.14 0.71 0.009
VMI motor coordination test	52.3 (13.6)	45–86	56.8 (10.6)	42–82	0.65 0.43 0.037

ANOVA results for differences between the FXS and FXS + autism groups on imitation scales

Table 2

	FXS + autism Mean (SD)	FXS Mean (SD)	df. 1	df. 2	F	p	$\eta^2$
Single face	6.82 (3.37)	9.09 (3.59)	1	18	1.65	0.216	0.084
Single hand	5.18 (2.52)	6.36 (2.50)	1	18	0.67	0.424	0.036
Complex hand	4.55 (1.97)	6.45 (3.01)	1	18	3.24	0.089	0.153
Movement sequences	13.45 (5.80)	16.18 (6.39)	1	18	0.70	0.416	0.037
Total imitation scale	30.00 (10.28)	38.09 (12.14)	1	18	2.06	0.169	0.102
Groping	12.30 (2.83)	7.30 (2.65)	1	18	19.16	0.001	0.545
Extraneous movement	17.30 (6.68)	10.20 (5.81)	1	18	5.53	0.032	0.257
Repetition	2.00 (1.76)	0.80 (1.03)	1	18	2.29	0.150	0.125
Mirrors	5.60 (4.43)	5.70 (4.81)	1	18	0.01	0.955	0.000
Bilateral error	1.80 (2.74)	1.10 (1.29)	1	18	0.27	0.613	0.016