

# “Everybody in the World Is My Friend” Hypersociability in Young Children With Williams Syndrome

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Williams syndrome (WS) is a rare genetic disorder involving a characteristic cardiac defect, typical facial appearance, and an uneven profile of cognitive strengths and weaknesses. WS is caused by a hemizygous deletion in chromosome band 7q11.23, including the gene for elastin (*ELN*). Typically, individuals with WS seem driven to greet and interact with strangers. The goal of the present study was to investigate age-related changes in the expression of hypersociability in WS. Parents of 64 children with WS, 31 children with Down syndrome (DS), and 27 normal controls (NC) provided data concerning specific aspects of their children's social behavior using the Salk Institute Sociability Questionnaire (SISQ). Children ranged in age from 1 year, 1 month to 12 years, 10 months. Consistent with earlier findings, whole group analyses showed the WS group to be significantly higher on all aspects of sociability studied. Comparisons among the groups at different ages revealed that hypersociability is evident even among very young children with WS, and, significantly, children with WS exceed children with DS with respect to Global Sociability and Approach Strangers in every age group. The findings from children who have the typical deletion for WS are contrasted with data obtained

from a young child with WS who has a smaller deletion and many physical features of WS, but who does not demonstrate hypersociability, providing intriguing clues to a genetic basis of social behavior in this syndrome. These data suggest the involvement of a genetic predisposition in the expression of hypersociability in WS. © 2003 Wiley-Liss, Inc.

**KEY WORDS:** hypersociability; Williams syndrome; development; genetic influence

## INTRODUCTION

Williams syndrome (WS) is a rare neurodevelopmental disorder arising from a hemizygous deletion in chromosome band 7q11.23, including the gene for elastin (*ELN*) and approximately 20 surrounding genes [Ewart et al., 1993; Korenberg et al., 2000]. Physical characteristics of WS include specific facial and physical anomalies (Fig. 1); a variety of cardiovascular difficulties, commonly supravalvular aortic stenosis; mild to moderate mental retardation; failure to thrive in infancy; and small stature [Bellugi et al., 2000; Morris and Mervis, 2000].

## Cognitive Characteristics of WS

From the perspective of cognitive neuroscience, the study of WS is particularly important because of the uneven profile of cognitive abilities observed in individuals with WS. For example, adults with WS tend to perform much better on tasks involving language as compared to tasks involving spatial processing abilities [Bellugi et al., 2001]. Expressive language abilities tend to be a strength in the face of mild to moderate mental retardation, whereas spatial abilities represent a specific disability, characterized by fractionated attention to detail at the expense of the whole, and a difficulty in integrating parts of a drawing or block design [Bellugi et al., 2000]. Further, even within the domain of visual processing, there is a major dissociation: individuals with WS have comparatively stronger abilities for re-

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## CHILDREN WITH WILLIAMS SYNDROME

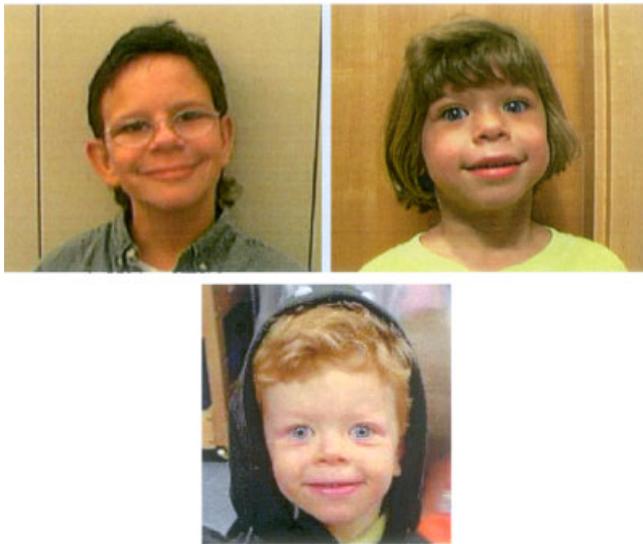


Fig. 1. Photographs of children with Williams syndrome (WS). (Used with permission). [Color figure can be viewed in the online issue, which is available at [www.interscience.wiley.com](http://www.interscience.wiley.com).]

cognizing and remembering faces despite their great difficulties in spatial cognition [Bellugi et al., 1999b]. Thus in WS, behavioral dissociations are not only observed across cognitive domains (e.g., language vs. space) but within domains as well (e.g., face vs. other spatial processing abilities). These dissociations are meaningful because the genetic basis of WS is known and therefore suggestive of the genetic underpinnings of these relative strengths and weaknesses in cognition and behavior.

### WS Genotype

More than 98% of individuals who are diagnosed as having WS by clinical evaluation and the probe for *ELN* have the same deletion breakpoints (Fig. 2). However, a very small number of persons diagnosed with WS have smaller deletions than are typical for the syndrome, all involving *ELN* but with a variable number of the surrounding genes also deleted [Donnai and Karmiloff-Smith, 2000; Korenberg et al., 2000]. Among these cases, the regions that are deleted differ from WS subjects with the “common” deletion that typically results in the loss of all genes from *FKBP6* through *GTF2i*. In addition, because the breakpoint in each individual with an atypical deletion is different, the genes that remain also differ among individuals with atypical deletions, as well as between the unusual cases and those with the more common type of deletion. Therefore, insofar as the different genes and pseudogenes contribute to the phenotypic outcome in WS, we may expect the individuals with different, small deletions may also have different behavior. Behavioral comparisons of individuals with atypical deletions to those whose deletions are typical will be crucial for shedding light on the links between genes and behavior.

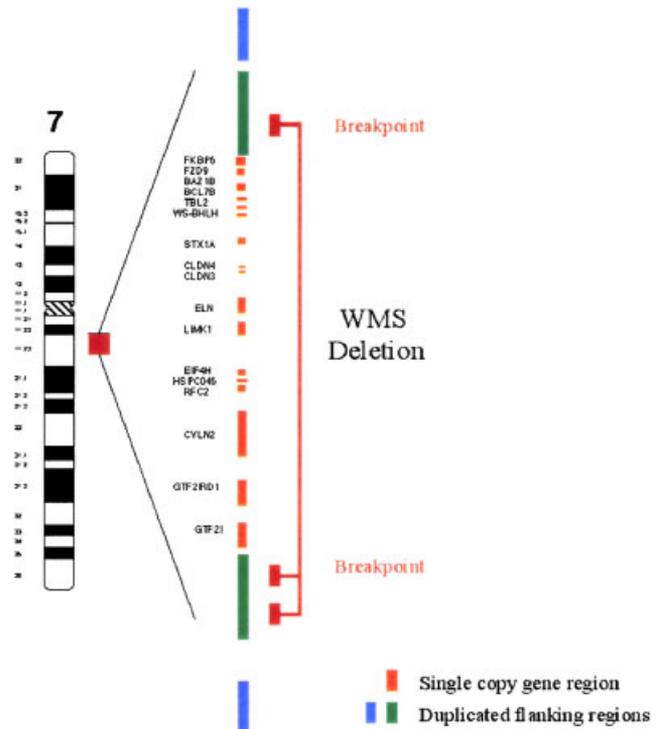


Fig. 2. The red box in the ideogram represents the region of chromosome 7, band 7q11.23, which is commonly deleted in WS. This region is expanded at the right to illustrate its genomic organization, a region of largely single-copy genes flanked by a series of genomic duplications (as indicated by bars) containing genes (e.g., *GTF2i*), pseudogenes (e.g., *GTF2iP*, *PMS2P*), and duplicate markers (e.g., *D7S489*). Bars at the end of the bracket indicate the regions used in the common breakpoints. [Color figure can be viewed in the online issue, which is available at [www.interscience.wiley.com](http://www.interscience.wiley.com).]

### Social Behavior in WS

A consistent behavioral characteristic of WS is hypersociability [see Jones et al., 2000 or Mervis and Klein-Tasman, 2000, for reviews]. Despite findings that they suffer from anxiety [Udwin et al., 1987; Dykens, 2003] and are significantly less well-adjusted socially than normal controls (NC) [Gosch and Pankau, 1994], researchers noted early on that the persons with WS have outgoing personalities [Von Armin and Engel, 1964]. This otherwise endearing characteristic can be a source of concern to parents of adolescents and adults with WS, as they report that their children appear unable to resist the temptation to approach strangers, and therefore may put themselves at risk for harm. Indeed, evidence from an experiment conducted with adults with WS has shown that they consistently and significantly rate photographs of faces higher in terms of approachability, regardless of the countenance expressed in the photograph, than do age-matched or younger NC children [Bellugi et al., 1999a].

Previous research in children with WS has examined sociability as an aspect of more global examinations of temperament or personality in WS. Within this larger context, children with WS have been described as “overly friendly” [Gosch and Pankau, 1997] compared to normal age-matched controls, and more “unreserved

with strangers" [Gosch and Pankau, 1994] as compared to children with non-specific mental retardation at the same chronological ages. Tomc et al. [1990] reported that children with WS are rated consistently higher in approach (as opposed to withdrawal) than either chronological- and mental-age-matched NC children. However, these studies did not directly compare children with WS to both typically developing and developmentally delayed controls on the same measures. In addition, although Gosch and Pankau [1997] reported that "over friendliness" was significantly and positively correlated with age, studies to date have not specifically examined sociability in children with WS from a developmental perspective.

We have assessed hypersociability among adolescents and adults with WS using a parental report questionnaire, the Salk Institute Sociability Questionnaire (SISQ) [Jones et al., 2000]. SISQ items measure the tendency to approach others, general behavior in social situations, the ability to remember names and faces, eagerness to please other people, the tendency to empathize with or comment on others' emotional states, and the tendency for other people to approach the subject. The questionnaire was completed by parents of adolescents and adults with WS or with Down syndrome (DS) and NC 13 years of age or older. Results showed that the subjects with WS were rated as being significantly more social overall than were subjects with DS or NC subjects. In contrast, there were no significant differences between the ratings for NC subjects and those with DS.

The present study sought to determine whether findings in young children would be similar to those observed for adolescents and adults, and how the pattern of social development proceeds across this age span. Using a cross-sectional design, we examined whether age-related changes occurred in the expression of sociability in children with WS and, if so, how these changes compared to changes observed in typically developing children and in children with DS, another genetically-based syndrome involving developmental delay. Importantly, this study examined the consistency and variability of sociability in children with WS which in turn allowed us to consider the expression of sociability not only in those with typical size deletions but also in children with atypical deletions. Such an examination may lead to illuminating a possible genetic pathway for hypersociability in WS.

## METHODS

### Subjects

The SISQ was completed by 64 parents of children with WS, 31 parents of children with DS, and 27 parents of NC. All children were between the ages of 1 year, 1 month and 12 years, 10 months. Children with WS were confirmed by fluorescence in situ hybridization (FISH) analysis to have hemizygous deletions for *ELN*. Children with DS were trisomy 21. The SISQ was distributed to parents of children with WS at a national meeting of the Williams Syndrome Association and

collected there or returned by mail. Parents of children with DS also returned by mail SISQs distributed at a National Down Syndrome Society meeting. In addition, data were collected from parents of children with WS or DS at the time their children came to our laboratory to participate in our ongoing research. Data for NC were collected from parents whose children attend a nearby elementary school. Informed, written consent was obtained from all participants according to the procedures prescribed by the Salk Institute's internal review board for research involving human subjects.

### Procedures

The SISQ is an exploratory experimental tool developed to measure various aspects of sociability commonly reported among people with WS [Jones et al., 2000]. It is a paper and pencil instrument in which parents are asked to rate their child's specific social abilities and tendencies on a seven-point Likert scale with low, mid, and high endpoint labels tailored to each individual item. In addition, parents were asked to provide qualitative descriptions of their child in various social situations. Questionnaire items were designed to provide a global measure of sociability and to measure two aspects of sociability, social approach behavior and social emotional behavior. The items that measure social approach behavior consist of statements such as "compare your child's tendency to approach strangers with an average child of the same age," and "my child would spontaneously greet or approach a member of his/her immediate family." Items assessing social approach behavior were grouped for analysis into two types: those items that assess the child's tendency to approach family members or others encountered frequently (an "Approach Familiars" score), and those items that assess the child's tendency to approach people unknown to them (yielding an "Approach Strangers" score). Social emotional items asked parents to rate their child's tendency to empathize with or comment on the emotional states of others, the accuracy of their emotional evaluations of others, their eagerness to please other people, and their abilities to remember names and faces of those they have met for the first time. For each subject, the Global Sociability score was the sum of 12 items; the Social Emotional score was the sum of 4 items; Approach Familiars, 3 items; and Approach Strangers, 5 items.

The quantitative data were first analyzed using all groups across the age span. In order to obtain a developmental perspective on hypersociability in WS, the data were analyzed a second time grouping the subjects by age into three categories: Youngest, <4 years old; Intermediate, 4 to <7 years old; and Oldest, 7 to <13 years old. These age groups were selected to roughly represent periods in a typical child's life in which the child's social contacts were primarily within family (Youngest); the child was in the initial stages of regular interactions with others outside the family, as in pre-school or kindergarten (Intermediate); and the child had become experienced interacting with others outside

the family (Oldest). Results of an analysis of variance (ANOVA) with age by syndrome revealed that the groups in the study were well matched for age (all comparisons *n.s.*,  $P > 0.05$ ). Mean ages and variances for each subject population within an age category are displayed in Table I.

In some instances, questionnaires were returned with items left blank. To minimize data loss, means were obtained for individual items according to the subject group and age, and these were inserted for missing values in the computation of Global Sociability and subscale scores. As an example, if a questionnaire for a 3-year-old child with WS was returned with an item left blank, the mean for that item for children with WS in the Youngest age group was used in the computation of the Global Sociability score and pertinent subscale scores. Only those questionnaires with a single item left blank were amended with the mean for that item and retained for analysis, which resulted in the loss of nine subjects from the study: five WS, three DS, and one NC. All of the attrition from the WS and NC groups occurred in the Youngest age category; two of the participants lost from the DS group also were in the Youngest age category. The third DS subject was 10 years, 7 months old. Among the questionnaires retained for analysis, six questionnaires in the Youngest group (three WS and three DS), five in the Intermediate group (three WS and two DS), and two in the Oldest group (one each WS and DS) utilized mean values for an individual item. Thus, the Youngest group comprised 13 WS, 14 DS, and 9 NC; the Intermediate group, 22 WS, 7 DS, and 9 NC; and the Oldest group, 24 WS, 7 DS, and 8 NC.

In the Whole group and each of the Age category analyses, the data were analyzed first by conducting an ANOVA with diagnostic Group as factor and Global Sociability as the dependent measure. This was followed by a multivariate analysis of variance (MANOVA) with Group as factor, and Social Emotional, Approach Familiars, and Approach Strangers scores as the dependent measures. With  $\alpha = 0.05$ , all post hoc comparisons were conducted using a Bonferonni correction to mitigate the probability of Type I errors resulting from multiple comparisons, thus, results are not reported as significant unless  $P \leq 0.0167$ .

Qualitative responses were evaluated by two independent raters, blind to the subjects' identities, who sorted the SISQs into three piles: shy, social, and in-between. Those in the social pile were then further sorted into a "least social" pile and a "most social" pile.

TABLE I. Means and Standard Deviations (SD) for Subject Populations Within Age Groupings

Group		WS	DS	NC
Youngest (<4 Years)	Mean	3.24	3.13	2.99
	SD	0.67	0.55	0.55
Intermediate (4 to <7 Years)	Mean	5.44	5.71	5.44
	SD	0.74	0.56	1.02
Oldest (7 to <13 Years)	Mean	9.76	9.10	9.45
	SD	1.93	2.48	1.92

Chi square analyses were used to determine whether the resulting frequencies in the characterization of responses were different among the three subject groups.

## RESULTS

### Whole Group Analyses

The Whole group ANOVA with diagnostic group as factor and Global Sociability as the dependent measure was highly significant [ $F(2,110) = 36.45$ ,  $P < 0.0001$ ]. The MANOVA with Group as factor, and Social Emotional, Approach Familiars, and Approach Strangers scores as dependent measures was also highly significant [Wilks' lambda = 0.47;  $F(6,216) = 16.68$ ,  $P < 0.0001$ ]. Inspection of the resulting ANOVA tables revealed significant results for each of the dependent measures. Table II summarizes the results of the univariate analyses.

As illustrated in Figure 3, the WS group significantly exceeded the NC group on all SISQ measures, and the WS group also exceeded DS on all but one measure (Approach Familiars). The DS and NC groups differed from each other on one measure, with NC significantly higher than DS on the Social Emotional score.

These differences were reflected qualitatively as well. For example, parents were asked to give examples of their "child's typical reactions when meeting someone for the first time." In response to this prompt, the parent of a 2 year, 7 month old NC child reported, "In the beginning, will turn face away but peek his eyes out and smile at them. A few minutes later, he'll interact." The parent of a 2 year, 7 month old child with DS wrote, "She would bury her head against my shoulder, cover her face partially with her hand, but look at the individual. Until it was time to part, then she will blow them a kiss and unbury her head and return to her usual sweet self." By contrast, the parent of a 2 year, 5 month old child with WS stated, "Gives hug—asks to be picked up." Table III provides additional examples from across the three age categories.

The representativeness of the qualitative responses with respect to diagnostic groups also was borne out statistically. Chi square analyses demonstrated highly significant differences among the proportions of qualitative responses for each subject group that were characterized as shy, social, and in between ( $\chi^2(4) = 64.06$ ,  $P < 0.0001$ ), and among those characterized as social, those considered least and most social ( $\chi^2(2) = 32.71$ ,  $P < 0.0001$ ). Specifically, a much greater proportion of the WS group than either DS or NC groups was rated social in the first Q-sort and, among the responses designated as social, a greater proportion of the WS group was characterized further as "most social." Table IV summarizes these results.

### Age Category Analyses

In the Youngest age category, the ANOVA examining Global Sociability was significant [ $F(2,33) = 10.57$ ,  $P < 0.0005$ ]. The MANOVA examining Social Emotional, Approach Familiars, and Approach Strangers in the Youngest group was also significant [Wilks'

TABLE II. Results of Whole Group Univariate Analyses

SISQ measures	DS M (SD)	NC M (SD)	WS M (SD)	F (2,110), P
Global Sociability	55.70 (11.05)	55.86 (10.17)	70.26 (7.23)	36.45, <0.0001
Social Emotional	16.63 (5.49)	20.17 (3.46)	22.48 (3.08)	21.62, <0.0001
Approach Familiars	19.02 (2.18)	18.23 (2.88)	20.07 (1.45)	7.94, 0.0006
Approach Strangers	15.11 (5.11)	11.99 (5.58)	21.20 (4.17)	41.50, <0.0001

lambda = 0.40, F(6,62) = 5.90, P < 0.0001]. Table V presents group means and standard deviations for each SISQ score and summarizes the results of the univariate analyses for the Youngest group, all of which were significant.

The results of the post hoc comparisons for the Youngest category are presented in Figure 4, which shows that the WS group was rated significantly higher than both the DS and NC groups on Global Sociability and Approach Strangers. In addition, the WS group was significantly higher than the NC group with respect to Approach Familiars, and WS was rated higher than DS on the Social Emotional measure. The DS group significantly exceeded the NC group with respect to Approach Familiars.

Table VI presents means and standard deviations, and summarizes the results of the univariate analyses

for the children in the Intermediate category. In this age range, statistically significant results were again obtained for Global Sociability [F(2,35) = 12.60, P < 0.0001]. The MANOVA was also highly significant [Wilks' lambda = 0.42, F(6,66) = 6.05, P < 0.0001]. As in all previous analyses, whenever statistically significant results were observed, the mean of the WS group was higher than the means of the other two groups.

Figure 5 presents the post hoc comparisons among the groups in the Intermediate age range. The groups were not statistically different with respect to Approach Familiars. There was one statistically significant comparison between the DS and NC groups, with NC exceeding DS on the Social Emotional measure. The WS group was significantly higher than both DS and NC on Global Sociability and Approach Strangers, and WS also exceeded DS on the Social Emotional measure.

BOX PLOTS OF WHOLE GROUP POST HOC ANALYSES

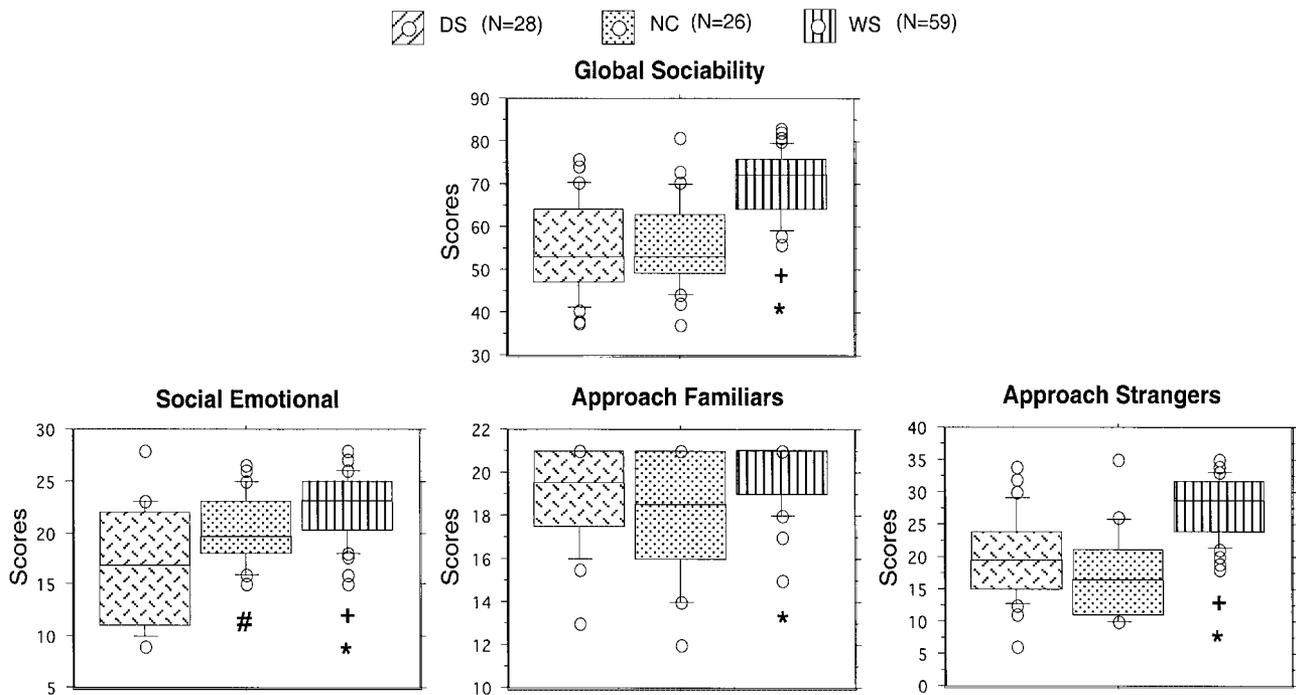


Fig. 3. Post hoc analyses of the data from across the age span revealed that the WS group significantly exceeded normal controls (NC) on all Salk Institute Sociability Questionnaire (SISQ) measures, and exceeded Down syndrome (DS) on all but one measure (Approach Familiars). The DS and NC groups differed from each other on the Social Emotional score, with NC significantly higher than DS. The graphs display horizontal lines at the 10th, 25th, 50th, 75th, and 90th centiles for each experimental group. Individual scores above the 90th or below the 10th centiles are plotted separately. +, WS/DS P ≤ 0.0167; \*, WS/NC P ≤ 0.0167; #, DS/NC P ≤ 0.0167.

TABLE III. Samples of Qualitative Responses to SISQ Item

NC (age)	DS (age)	WS (age)
He's curious, but not outgoing. Kind of reserved. Not real social. (2y, 2m)	Will walk into a room of strangers and go play with toys. (2y, 5m)	When we are going through a checkout at the grocery, will smile and say "Hi!" He will then either offer the stranger something from the cart or reach out to them. (2y, 1m)
Usually, hide under mom's legs or put face in mom's neck. (3y, 9m)	She'll say "Hi." Give smiles. (3y, 6m)	At restaurants she goes to other tables and gets right in their face and says "Hi!" (4y, 1m)
Notices an adult interact with a child, smiles, offers info relevant to self—"I have one of those—she's so cute" "My sister can do that." (5y, 5m)	Says hello to them. Says, "How are you doing?" Sometimes shy at first. Greet them and shake hands. In elevator, says "Hi" to people. Same at church. (5y, 1m)	Will "butt in" on others' conversations in grocery store, library, wherever. Always asks name then will attempt to engage in further conversation by asking if they have any pets or if they are going to do whatever we are doing. (5y, 8m)
Shy, has to be told to say hello. Getting better as he gets older about conversation. Does not make eye contact, embarrassed to speak. (7y, 0m)	Initially is usually shy—once she feels comfortable, she will respond verbally. (7y, 11m)	Socializes with anyone she meets. In church she recognizes a new member or someone visiting and says, "I don't know them—I need to know them." Also in grocery store it would take me hours to get my shopping done as my daughter would say hi and ask questions to every person we passed. (7y, 5m)
It depends on the location and whether or not there are others around. (11y, 0m)	Child doesn't really approach unless prompted to do so. (10y, 0m)	She will greet them, ask them their names and if they have kids, dogs, or cats. Carries on conversations. Will hug them before they go. (10y, 6m)

Give some examples of your child's socializing with strangers. Y, year; m, month.

TABLE IV. Data Summary for Chi Square Analyses

Characterized as	Percentage of responses		
	DS	NC	WS
Shy	13	28	1
In between	35	33	10
Social	52	39	89
Least social	80	76	45
Most social	20	24	55

The Global Sociability ANOVA for the Oldest age category was also significant [ $F(2,36) = 14.39$ ,  $P < 0.0001$ ]. The MANOVA, too, was highly significant [Wilks' lambda = 0.40,  $F(6,68) = 6.11$ ,  $P < 0.0001$ ]. Table VII presents group means, standard deviations, and ANOVA summaries for the Oldest age category. All analyses yielded significant results and, as before, in every instance the means of the WS group were higher than either DS or NC.

The post hoc comparisons for the Oldest group are shown in Figure 6. In the Oldest age category, the WS group significantly exceeded the NC group on all measures. The WS group was rated significantly higher than the DS group on Global Sociability and Social Emotional scores. The DS and NC groups were significantly different from each other only in terms of Approach Strangers, with DS receiving higher scores than NC.

Age-related differences in the expression of sociability, both within and across subject populations, were revealed when subjects were grouped by age. Graphing the results of the age group comparisons shows that development with respect to the various measures of sociability follows different, distinct paths in the three groups (Fig. 7). Among the NC children, significant differences were observed between the Youngest and Intermediate groups, and between the Intermediate and Oldest groups on the measure of Global Sociability. The measure of Approach Strangers followed a similar pattern in NC, although, in this case, the difference between the Intermediate and Oldest age categories only approached significance. No statistical difference was observed between the Youngest and the Oldest groups of the NC children on these measures, however. The age-related differences observed for the NC group thus resemble an inverted U function. In contrast, the children with WS differed significantly on Global Sociability and Approach Strangers when comparing the Youngest group to either the Intermediate or Oldest groups, but the Intermediate and Oldest groups were not statistically different from each other. In other words, children with WS showed a significant increase in Global Sociability and Approach Strangers from the Youngest to the Intermediate groups, and the increase in these measures was maintained into the Oldest group when, in the NC group, these measures began to decline. Finally, no statistically significant age-related changes were observed in the DS sample on these measures. In general, the pattern of age-related changes observed in the WS and DS groups appear similar in form, but the

TABLE V. Univariate Analyses Results for the Youngest Age Category (<4 Years)

SISQ measures	DS M (SD)	NC M (SD)	WS M (SD)	F (2,41), P
Global Sociability	53.36 (10.91)	49.33 (6.36)	64.54 (5.59)	10.57, 0.0003
Social Emotional	16.18 (4.94)	19.56 (3.58)	20.61 (3.48)	4.17, 0.02
Approach Familiars	18.61 (2.63)	16.11 (2.52)	19.46 (1.71)	5.84, <0.01
Approach Strangers	18.57 (7.16)	13.67 (3.90)	24.47 (4.43)	10.29, 0.0003

WS group starts out and remains significantly higher than DS.

DISCUSSION

The findings above provide evidence that the behavior within the domain of sociability in WS is distinct from that seen in typically developing children and in children with DS. These findings are particularly important because the differences in hypersociability, particularly the attraction to strangers, cannot be attributed simply to cognitive impairment resulting in a lack of understanding of the social conventions governing contact with others, as both WS and DS are cognitively impaired. Indeed, it was not unusual for the parents of children with DS to report a coy friendliness toward others; in most cases, this was described as a tentative expression of interest in other people that could develop into interaction if the child received reciprocal encouragement. The children with WS, however, required no encouragement from anyone to initiate and continue contact with others; they seemed to be driven to engage strangers. In the Whole group

analysis, children with WS were reported higher on all but one aspect of sociability measured, Approach Familiars, when compared with chronologically age-matched children with DS. The WS group also exceeded the same age NC group on all measures.

As was illustrated in the contrast of subject groups by age, the WS group at all ages evidenced little variability with respect to approach behavior. This reduced variability in the WS group was also evident in qualitative sorts and related chi square analyses. These results, coupled with the early age of onset, suggest that a predisposition toward hypersociability, particularly the tendency to approach strangers, may be an innate characteristic of WS. The contributions of specific genes to this characteristic may be inferred by comparing children with typical deletions for WS to those with smaller, atypical deletions.

Toward Identifying the Genes for Sociability in WS?

As noted in the "Introduction," WS is caused by the deletion of one copy of a very small set of genes and

BOX PLOTS OF YOUNGEST CATEGORY POST HOC ANALYSES

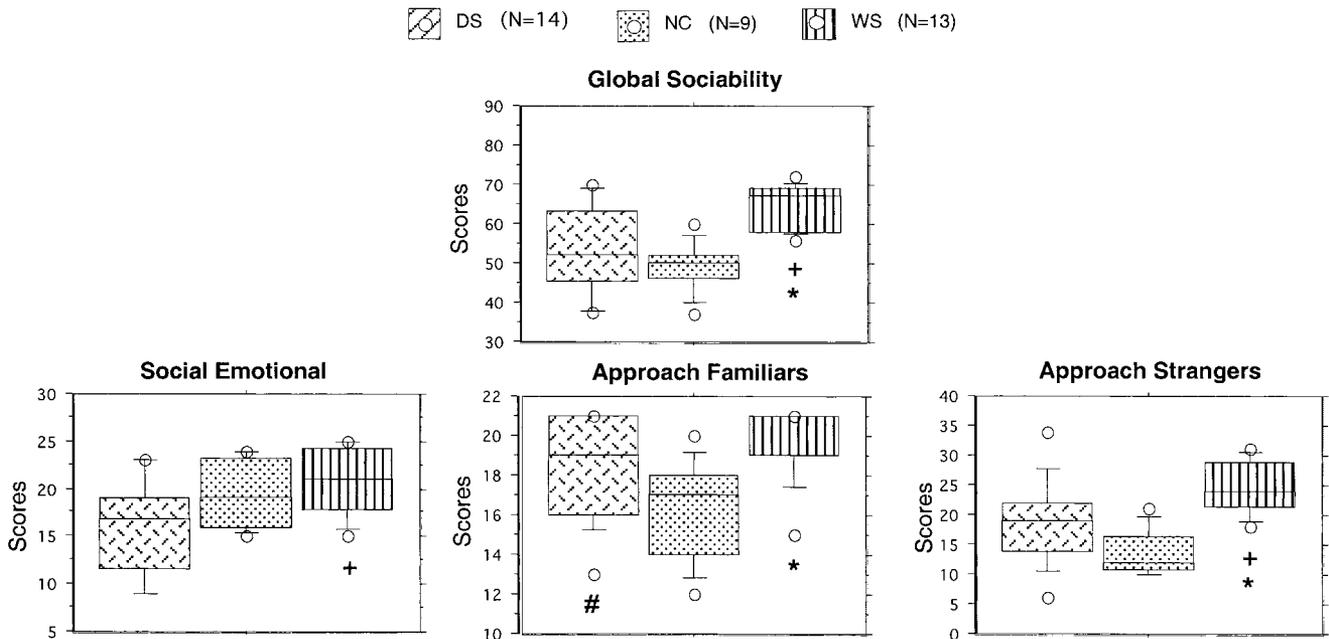


Fig. 4. Post hoc analyses of the data from the Youngest group showed WS rated significantly higher than both DS and NC on Global Sociability and Approach Strangers. In addition, WS was significantly higher than NC on Approach Familiars, and higher than DS on the Social Emotional measure. DS significantly exceeded NC on Approach Familiars. The graphs display horizontal lines at the 10th, 25th, 50th, 75th, and 90th centiles for each experimental group. Individual scores above the 90th or below the 10th centiles are plotted separately. +, WS/DS  $P \leq 0.0167$ ; \*, WS/NC  $P \leq 0.0167$ ; #, DS/NC  $P \leq 0.0167$ .

TABLE VI. Univariate Analyses Results for the Intermediate Age Category (4 to <7 Years)

SISQ measures	DS M (SD)	NC M (SD)	WS M (SD)	F (2,35), P
Global Sociability	54.69 (11.60)	63.61 (8.59)	71.78 (6.59)	12.60, <0.0001
Social Emotional	16.19 (7.59)	21.39 (3.48)	22.70 (2.46)	6.94, <0.003
Approach Familiars	18.86 (1.68)	20.33 (1.41)	20.04 (1.56)	2.04, n.s.
Approach Strangers	19.64 (5.71)	21.89 (6.81)	29.03 (3.86)	12.57, <0.0001

pseudogenes, numbering fewer than 20, at 7q11.23 [Korenberg et al., 2000]. Nearly all clinically identified individuals with WS lack precisely the same set of genes, with breakpoints at the same places. Occasionally, individuals with WS are identified who have somewhat smaller deletions; such cases are potentially very meaningful as a way of providing clues to the roles of specific genes in the behavioral expression of the syndrome. For example, it seems clear that lacking one copy of *ELN* is associated with supravalvular aortic stenosis, cardiovascular defect that is typical of the disorder [Li et al., 1997]. In an effort to link genotype to behavioral phenotype, it has been argued that hemizygosity for the gene *LIMK1* may be the basis of the spatial deficit in WS [Frangiskakis et al., 1996], although the relevance of *LIMK1* in this regard is disputed [Donnai and Karmiloff-Smith, 2000]. Recently, we studied a child who was clinically diag-

nosed with WS and lacks one copy of *ELN* along with most of the contiguous genes usually associated with the deletion for WS. However, this child has at least one gene present on the extreme end of the WS region that is typically missing in WS. We turn next to this case.

### WS With a Smaller Deletion and Social Behavior

Subject 5889 is a 2 year, 6 month old girl with many representative physical characteristics of WS including short stature, typical facial appearance, and supravalvular aortic stenosis. However, using a subset of 21 BAC probes with FISH [Chen and Korenberg, 2001], we defined the region deleted in 5889 as atypical. The region deleted in 5889 begins from the centromeric region of the common deletion, and includes the genes *FKBP6* and *FZD9*, but it does not include the most

### BOX PLOTS OF INTERMEDIATE CATEGORY POST HOC ANALYSES

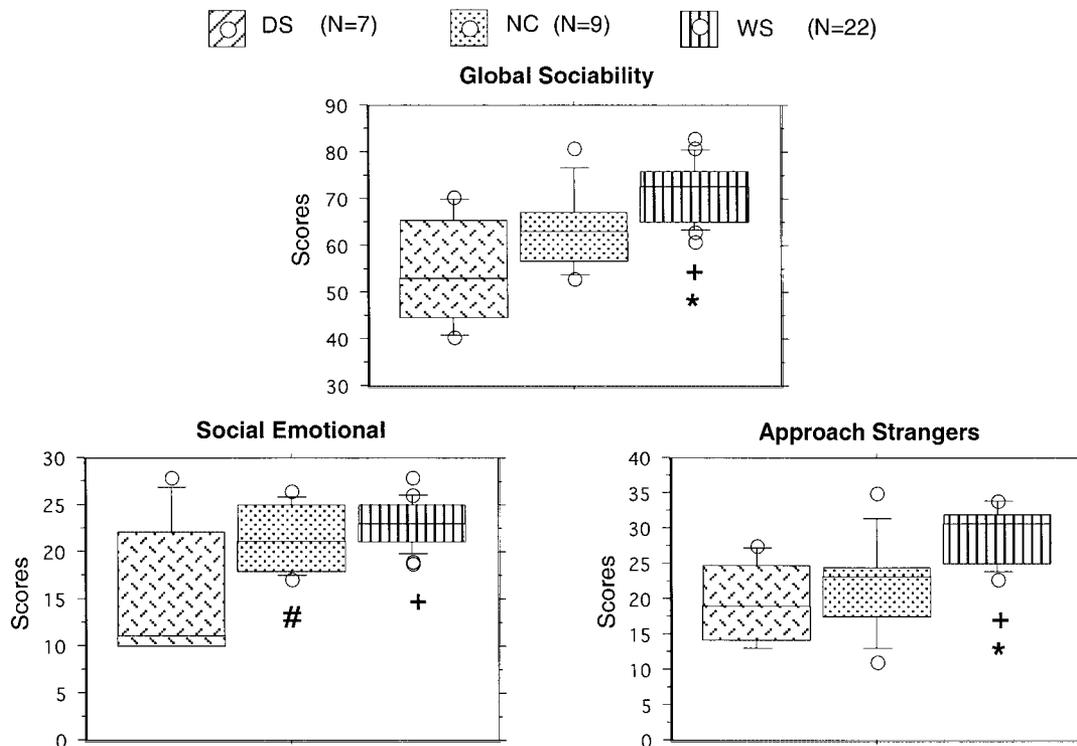


Fig. 5. The post hoc comparisons for the Intermediate groups revealed that the WS significantly exceeded NC and DS on Global Sociability and Approach Strangers. In addition, WS and NC were rated significantly higher than DS on Social Emotional. There were no statistical differences among the groups with respect to Approach Familiars. The graphs display horizontal lines at the 10th, 25th, 50th, 75th, and 90th centiles for each experimental group. Individual scores above the 90th or below the 10th centiles are plotted separately. +, WS/DS  $P \leq 0.0167$ ; \*, WS/NC  $P \leq 0.0167$ ; #, DS/NC  $P \leq 0.0167$ .

TABLE VII. Univariate Analyses Results for the Oldest Age Category (7 to &lt;13 Years)

SISQ measures	DS M (SD)	NC M (SD)	WS M (SD)	F (2,36), P
Global Sociability	61.40 (10.23)	54.50 (10.24)	71.96 (7.23)	14.39, <0.0001
Social Emotional	17.98 (4.73)	19.50 (3.38)	23.29 (3.06)	8.27, 0.001
Approach Familiars	20.00 (1.41)	18.25 (2.92)	20.42 (1.10)	5.12, 0.01
Approach Strangers	23.43 (5.47)	16.75 (5.65)	28.25 (4.67)	16.20, <0.0001

telomeric region, defined by the gene for *GTF2i*, and possibly also *GTF2iRD1* and *CYLN2*. Thus, 5889's deletion in 7q11.23 is unusually small: a subset of genes located at the telomeric region are present in this child that are typically absent in individuals with WS [Korenberg and Chen, 2001].

Subject 5889 is also different with respect to social behavior, showing little of the hypersociability that is typical of WS. In fact, researchers noted that she is shy when meeting strangers, hiding behind her mother's skirt as would a normal child of her age, and very unlike nearly all typical WS children who are hypersocial from the outset. Her unusual behavior with respect to sociability was also amply evident in her measurements on the SISQ.

The ratings made by Subject 5889's parents concerning her social behavior were decidedly atypical, specifically with regard to WS approach behavior. As depicted in Figure 8, converting her scores to z-scores for comparison with the WS group in the Youngest age range, 5889's Social Emotional score was not statistically different from the rest of the group ( $z = -0.74$ ), nor

was her Approach Familiars score ( $z = -0.88$ ). However, 5889's Global Sociability score was significantly different ( $z = -2.59$ ), as was her score for Approach Strangers ( $z = -2.39$ ). By way of comparison, the next lowest z-scores for Global Sociability and Approach Strangers among the WS group in the Youngest age category were  $-1.57$  and  $-1.48$ , respectively, neither of which is significantly different. In sum, 5889's parents rated her consistently less social than the parents of other children with WS rated her peers, and the difference was attributable to her lack of approach toward strangers. Qualitatively, her parents were at a loss to respond when given the prompt, "Please give examples of spontaneous and unsolicited overtures to strangers made by your child." Subject 5889's mother did not understand the motivation for the question, whereas time and again, parents of other children with WS have read the question, smiled, then related numerous, lengthy instances of extreme sociability that characterized their child with WS.

These findings provide the framework for investigating the neurobiological and genetic bases of social

## BOX PLOTS OF OLDEST CATEGORY POST HOC ANALYSES

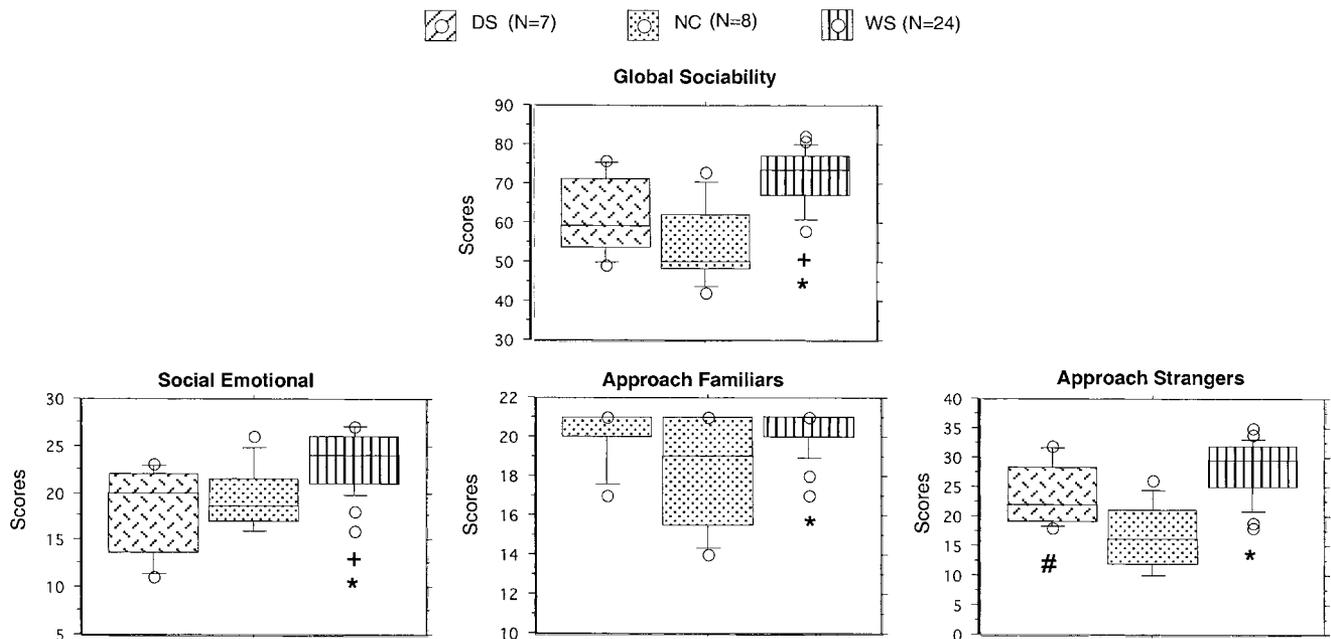


Fig. 6. The post hoc comparisons for the Oldest groups revealed that WS significantly exceeded NC on all measures. WS was rated significantly higher than DS on Global Sociability and Social Emotional. DS and NC were significantly different only on Approach Strangers, with DS receiving higher scores. Each graph displays horizontal lines at the 10th, 25th, 50th, 75th, and 90th centiles for each experimental group. Individual scores above the 90th or below the 10th centiles are plotted separately. +, WS/DS  $P \leq 0.0167$ ; \*, WS/NC  $P \leq 0.0167$ ; #, DS/NC  $P \leq 0.0167$ .

AGE-RELATED CHANGES IN GLOBAL SOCIABILITY AND APPROACH STRANGERS BY SUBJECT POPULATION

YOUNGEST
  INTERMEDIATE
  OLDEST

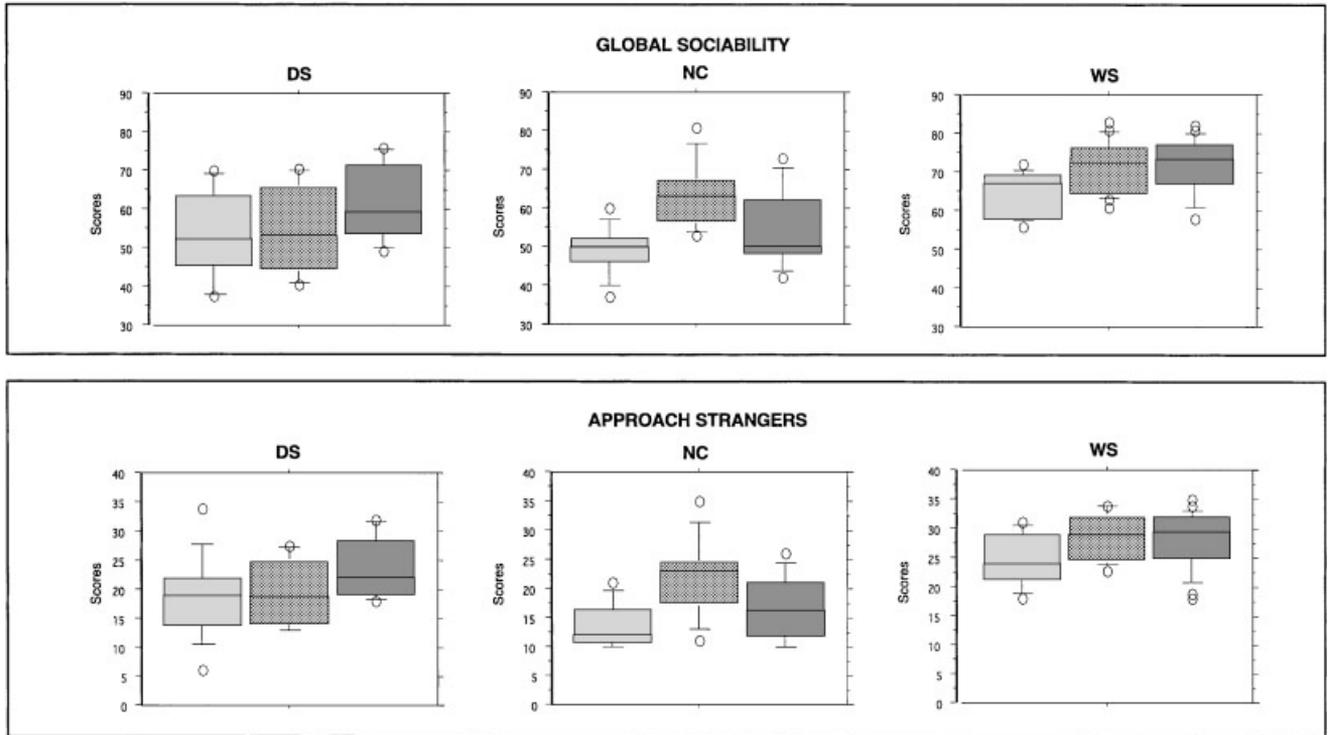


Fig. 7. Each graph displays horizontal lines at the 10th, 25th, 50th, 75th, and 90th centiles for each experimental group. Individual scores above the 90th or below the 10th centiles are plotted separately. Note three, distinct patterns of age-related change among the experimental groups. For NC children, differences were observed between the Youngest and Intermediate groups, and between the Intermediate and Oldest groups, on the measures of Global Sociability and Global Approach, but there was no statistical difference between the Youngest and Oldest groups. Children

with WS differed significantly on these measures when comparing the Youngest group to either the Intermediate or the Oldest groups, but the Intermediate and Oldest groups were not statistically different from each other. No statistically significant age-related changes were observed in the DS sample on these measures. In general, the pattern of age-related changes observed in the WS and DS samples appear similar to each other and different from NC, but the WS sample starts out and remains significantly higher than DS.

behavior, especially affiliative behavior, in WS. Further analysis of Subject 5889's deletion and behavior, and that of others like her, is the focus of our ongoing research.

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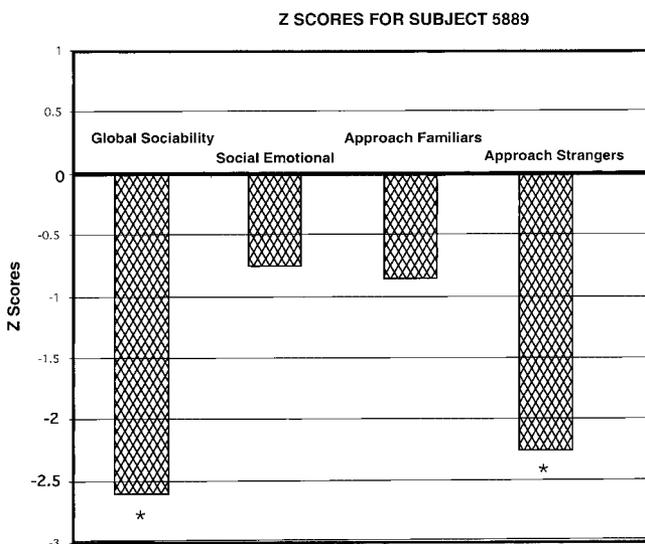


Fig. 8. Subject 5889's SISQ scores were converted to z-scores for comparison with the WS group in the Youngest age range. The heavy line at zero indicates the Youngest WS group mean. 5889's Global Sociability and Approach Strangers scores were significantly lower than the group means for those measures. Her Approach Familiars and Social Emotional scores were not different from the Youngest WS group. \*,  $P \leq 0.05$ .

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