Cognitive abilities in siblings of children with autism spectrum disorders

ARTICLE *in* EXPERIMENTAL BRAIN RESEARCH · APRIL 2014

Impact Factor: 2.17 · DOI: 10.1007/s00221-014-3935-8 · Source: PubMed

5 AUTHORS, INCLUDING:

Valentina Gizzonio
Università degli studi di Parma
3 PUBLICATIONS **6** CITATIONS
SEE PROFILE

Pietro Avanzini
Università degli studi di Parma
26 PUBLICATIONS **70** CITATIONS
SEE PROFILE

Maddalena Fabbri-Destro
Istituto Italiano di Tecnologia
26 PUBLICATIONS **1,144** CITATIONS
SEE PROFILE

Cristina Campi
Italian National Research Council
20 PUBLICATIONS **87** CITATIONS
SEE PROFILE

Exp Brain Res
DOI 10.1007/s00221-014-3935-8

RESEARCH ARTICLE

Cognitive abilities in siblings of children with autism spectrum disorders

Valentina Gizzonio · Pietro Avanzini · Maddalena Fabbri-Destro · Cristina Campi · Giacomo Rizzolatti

Received: 23 December 2013 / Accepted: 24 March 2014

Abstract The aim of the present study was to assess the *cognitive profiles* of children with autistic spectrum disorder and of their healthy siblings (Siblings). With the term *cognitive profile*, we indicate the relationship extant among the values of verbal and performance subtests of the Wechsler Intelligence Scale. The conducted statistical analyses indicated that, although siblings showed a normal intelligent quotient and did not differ in this aspect from typically developing group, their *cognitive profile* was amazingly similar to that of their relatives affected by autism. A *k*-means clustering analysis on the values of single subtests further confirmed this result, showing a clear separation between typically developing children on the one side, and autistics and their siblings on the other. We suggest that the common cognitive profile observed in autistic children and their siblings could represent a marker of liability to autism and, thus, a possible intermediate phenotype of this syndrome.

Keywords Autism · Siblings · Cognitive profile · Endophenotype · WISC

Introduction

There is a large number of studies that investigated the IQ profile of children with autistic syndrome disorder (ASD). All of them reported that children with autism typically present an IQ profile determined by the Wechsler Intelligence Scale (Wechsler 1974, 1991), with strengths in performance over verbal abilities (Lockyer and Rutter 1970; Asarnow et al. 1987; Narita and Koga 1987; Ohta 1987; Schneider and Asarnow 1987; Allen et al. 1991; Girardot et al. 2012; for a review see Siegel et al. 1996; Ankenman et al. 2014).

Some studies, besides determining the IQ profile (verbal vs. performance values), focused on the scores found in the different verbal and performance subtests (*cognitive profile*). These studies consistently reported low scores for children with autism in Comprehension subtest of the Verbal Scale, and in Coding subtest in Performance Scale. Less consistent results were found for Block Design subtest. While some studies reported "peaks" in this subtest (Freeman et al. 1985; Lincoln et al. 1988; Shah and Frith 1993; Happé 1994; Dennis et al. 1999; Mayes and Calhoun 2003; Caron et al. 2006), others did not confirm such observation (Szatmari et al. 1990; Ozonoff et al. 1991; Ehlers et al. 1997; Ropar and Mitchell 2001; Kaland et al. 2007; Charman et al. 2011; for a review see Ankenman et al. 2014).

First degree relatives of individuals diagnosed with autism often show pathological traits qualitatively similar, but much milder in severity, compared to those present in their affected siblings (Piven et al. 1997). On the contrary, contrasting results are reported for visual emotion recognition abilities (Losh et al. 2009; Neves et al. 2011; see, however, Buitelaar et al. 1999; Castelli 2005) and executive functions (Hughes et al. 1999; Delorme et al. 2007; Kawakubo et al. 2009; see, however, Ozonoff et al. 1993). While the investigation of the cognitive profile of autistic children by means of Wechsler Intelligence Scales returned, as discussed above, a rather clear pattern, contrasting results were provided by the same test conducted on siblings of children with autism. While earlier studies reported an elevated rate of cognitive deficits

V. Gizzonio · P. Avanzini · C. Campi · G. Rizzolatti (✉)
Dipartimento di Neuroscienze, Sezione di Fisiologia, Università di Parma, Via Volturno, 39/E, 43100 Parma, Italy
e-mail: giacomo.rizzolatti@unipr.it

M. Fabbri-Destro · G. Rizzolatti
Brain Center for Social and Motor Cognition, Italian Institute of Technology, Via Volturno, 39/E, 43100 Parma, Italy

Published online: 08 April 2014

among the siblings of autistic children (August et al. 1981; Minton et al. 1982), more recent studies did not show any difference between siblings and control groups (Freeman et al. 1989; Szatmari et al. 1993; Pilowsky et al. 2007).

A discrepancy between verbal and performance abilities, characteristic of autism, was found in siblings of children with autism by Minton et al. (1982), who reported that scores on various verbal subtests were significantly lower than scores on performance ones. Low scores on verbal subtests were also reported by Leboyer et al. (1995). In contrast, Fombonne et al. (1997) found no specific cognitive profile in the relatives of children with autism, and no selective impairment of verbal relative to performance scores was found.

The majority of these studies were conducted using Wechsler Intelligence Scale-Revised (WISC-R, Wechsler 1974) (August et al. 1981; Minton et al. 1982; Leboyer et al. 1995; Fombonne et al. 1997; Folstein et al. 1999). Furthermore, some of them were performed using either only few of the WISC subtests (Leboyer et al. 1995; Fombonne et al. 1997; Pilowsky et al. 2007) or four indexes only [Verbal Comprehension (VCI), Perceptual Organization (POI), Freedom from Distractibility (FDI), and Processing Speed (PSI)] (Pilowsky et al. 2007).

Thus, at present, there is no clear picture of the cognitive profile of siblings of children with autism, as shown by Wechsler Scales, and it is still an open question whether this IQ profile is shared by their affected siblings. The presence of some similarities between the two populations could reflect a cognitive endophenotype of autism and provide indications useful for the cognitive assessment of a heterogeneous syndrome like autism. In the present study, we addressed this issue by administering the WISC-III (Wechsler 1991) and comparing the cognitive profiles of autistic children with their siblings and with typically developing children (TD) as a control group. The affected–unaffected sibling design is a common approach in endophenotype research (Almasy and Blangero 2001; Waldman 2005), given that siblings share on average of 50 % of genes with their affected brother (Oerlemans et al. 2013), even if they do not develop the syndrome. The assumption of the design is that psychiatric disorders are caused by a complex interplay between multiple susceptibility genes and environmental factors (Gottesman and Gould 2003), so it could allow one to identify subtle signs of the disorder, common with their affected relatives, and consequently to isolate the ones genetically based.

Materials and methods

Participants

A total number of 95 children took part in the study. Thirty-one were children with diagnosis of autism spectrum disorder (ASD), 21 were siblings of these children (Siblings), and 43 were children with typical development (TD). The study was approved by the Local Ethical Committee (Comitato Etico Unico per la Provincia di Parma) and was conducted according to the Helsinki declaration. Written informed consent was obtained from parents of each child involved in the study.

ASD

The age of autistic group (23 males and 8 females) ranged between 6 and 14 years (mean 9.03 years; SD 2.61 years). They were recruited in four different Italian centers: (1) Pediatric Neuropsychiatry of Unità Sanitaria Locale 11, Empoli, (2) The rehabilitation center for autism "Centro Mai Soli", Genoa, (3) Institute of Rehabilitation "Villaggio Eugenio Litta," Grottaferrata, Rome, and (4) The Autism Center of Parma. All children met diagnostic criteria for autistic disorder according to the clinical criteria of Diagnostic and Statistical Manual of Mental Disorders, fourth edition—Text Revised (American Psychiatric Association 2000). The diagnosis was then confirmed by experienced clinicians by means of the Autism Diagnostic Observation Schedule (Lord et al. 1989). Its scores indicated that 19 out of 31 children met the criteria for autistic disorder, while the remaining 12 met the criteria for autism spectrum disorder. Note that, given their well-known and peculiar IQ profile (VIQ > PIQ), no children diagnosed as Asperger were included in this group. According to their medical records, all patients were free from any evident neurological abnormality as well as from hearing or visual impairment.

Siblings

Twenty-one typically developing siblings of autistic children (12 males and 9 females) between 6 and 16 years of age (mean 9.86 years; SD 2.66 years) participated in the study. The siblings' sample had no reported history of psychiatric disturbances, learning disabilities, or neurological disorders.

TD

Control group comprised 43 typically developing children (16 males and 27 females) between 6 and 11 years of age (mean 7.88 years; SD 1.73 years). They were recruited in a primary school in Teramo. Similarly to Siblings, the control sample had no reported history of psychiatric treatment, learning disabilities, or neurological disorders.

All children were tested by a clinical psychologist with the Wechsler Intelligence Scale for Children-3rd edition (WISC-III, Wechsler 1991; for Italian standardization see Orsini and Picone 2006). Note that the most recent version

of WISC (WISC-IV, Wechsler 2003) is not yet in clinical use in most pediatric neurology centers in Italy, because the Italian normative sample of this version has been published in 2012. While the testing of children of ASD was carried out in the above-mentioned clinical centers, Siblings and TD were examined by a clinical psychologist, and a second psychologist, blinded to the group, performed the scoring.

In order to evaluate social abilities and compare them among groups, we asked all parents to fill the SRS questionnaire. The tests relative to 74 out of 95 children (41 TD; 16 Siblings; 17 ASD) were collected.

Tests

Wechsler Scales

The Wechsler Intelligence Scale for Children (WISC) provides the IQ score (Full Scale Intelligence Quotient—FSIQ), computed combining the scores of the Verbal and Performance Scales. Each of these scales provides a score (VIQ and PIQ, respectively) indexing the global verbal and performance functioning. The discrepancy between VIQ and PIQ quantifies a possible unbalance between these cognitive abilities. A value equal to or greater than 15 points is considered a clinically significant marker.

In accord with the clinical practice of the four clinical centers that collaborated in the study, we administered to Siblings and TD the WISC-III. Five verbal and five performance subtests form the core of WISC-III. The verbal subtests are as follows: Information (IN), Similarities (SM), Arithmetic (AR), Vocabulary (VO), and Comprehension (CM). The performance subtests are as follows: Picture Completion (PC), Coding (CD), Picture Arrangement (PA), Block Design (BD), and Object Assembly (OA). The scores relative to each subtest were normalized according to normative Italian sample of 2,200 children, equally subdivided according to the age in the 6–16 years old range (Orsini and Picone 2006).

Social Responsiveness Scale

The Social Responsiveness Scale (SRS) (Constantino and Gruber 2005, see also Hus et al. 2013a, b; Constantino et al. 2013) is a quantitative measure of autistic traits in 4- to 18-year-olds, which has been used in behavior-genetic, epidemiological, and intervention studies. SRS inquires about a child's ability to engage in emotionally appropriate reciprocal social interactions in naturalistic settings and includes items that ascertain social awareness, social information processing, capacity for reciprocal social responses, social anxiety/avoidance, and characteristic autistic preoccupations/traits.

Statistical analysis of WISC-III data

The aim of our work was to determine whether Siblings share some cognitive aspect with ASD population. All the following multifactorial ANOVAs will consider Group (TD, Siblings, ASD) and Sex (M, F) as between-subjects factors. When significant effect was found, post hoc analyses with Bonferroni correction for multiple comparisons were conducted.

The effects of these factors were evaluated: (1) on the age of the participants in order to assess the homogeneity of the sample; (2) on the FSIQ to evaluate the global cognitive functioning of each population and so to rule out a general and unspecific cognitive impairment of Siblings with respect to the control population; (3) on VIQ and PIQ scores, separately, to investigate whether and to what extent the overall verbal and performance abilities varied among the three groups.

An additional repeated measurements ANOVA was employed to estimate the relationship between Verbal and Performance Scales over the three populations. To this aim, besides the above-mentioned factors, the Scale (VIQ, PIQ) was considered as within-subjects factor. This analysis allowed us to compare each population with the values typically considered to be clinically relevant. Note that a difference of 15 points is the threshold considered to indicate a significant VIQ or PIQ prevalence.

As already mentioned, we call *cognitive profile* the pattern of the child scores for all subtests belonging to each Scale. As our aim was to evaluate the cognitive profile *regardless the global functioning*, for each subject, we zero-mean-centered the profile within each scale (Verbal and Performance) via the subtraction of the average of all the scores. This normalization procedure was applied within each scale so that, for instance, the relative verbal scores were not biased by global Performance Scale level. By this approach, the shape of the profile with its strengths and weaknesses remained unmodified, while comparable in terms of amplitude of the different item values.

In order to determine significant strengths and weaknesses peculiar to each group, a one-sample t test was calculated versus a zero-mean distribution. We labeled: "strengths" the values significantly higher than zero and "weaknesses" the values significantly lower than zero. This procedure was applied to each subtest and group, separately, as no a priori assumption was made on strengths and weaknesses specific for each population. Results were corrected for the number of considered subtests, i.e., they were considered significant if p value resulted to be lower than 0.01. In addition, we computed the statistical power for all the t tests, taking into account the mean values and the standard deviation of each subtest, as well as the alpha value (0.01) and the sample size. A distinctive cognitive

Table 1 Participants

	Typical development	Siblings	ASD
Sample size	42 (m: 15; f: 27)	21 (m: 12; f: 9)	31 (m: 23; f: 8)
Chronological age	M 7.88; SD ± 1.73	M 9.86; SD = ±2.66	M 9.03; SD ± 2.61
Full Scale Intelligence Quotient (FSIQ)	M 114; SD ± 8.80	M 107; SD ± 11.80	M 79.74; SD ± 17.09
Verbal IQ (VIQ)	M 116; SD ± 10.6	M 101; SD ± 14.5	M 74.19; SD ± 20.18
Performance IQ (PIQ)	M 108; SD ± 9.1	M 111; SD ± 10.8	M 90.09; SD ± 18.19
VIQ-PIQ	+8	−10	−16
ADOS Communication Subscale	N.A.	N.A.	M 4.74; SD ± 2.04
ADOS Social Subscale	N.A.	N.A.	M 7.83; SD ± 2.84

Characteristics of typically developing children (TD), Siblings and children with autism (ASD) are reported. The sample size, chronological age, Full Scale Intelligent Intelligence Quotient (FSIQ), Verbal Intelligence Quotient (VIQ), Performance Intelligence Quotient (PIQ), VIQ and PIQ difference and Autism Diagnostic Observation Schedule (ADOS) modules 2 and 3—Communication Subscale and Social Subscale—scores are reported

profile of strengths and weaknesses, at the subtest level, was obtained for each group.

Significant weaknesses identified for ASD population were further characterized testing the possible correlation with the age and the symptoms severity of the patients. To this aim, a Pearson correlation was computed.

Clustering analysis

In order to assess the specificity of the different profile for each group within the entire sample, a clustering analysis was performed. The data set for the cluster was formed by the 10-scores relative profiles from both the Verbal and the Performance Scales for all participants. A *k*-means clustering algorithm (Anderberg 1973), blind to each subject population, was employed, and the number of clusters was fixed at three, i.e., a number equivalent to the included populations. Due to the random initialization of the clusters, we run a very high number of trials (1,000) of the clustering algorithm to ensure that results were independent of a random initial setting of the clusters. For each run, we considered as representative of a given population each cluster with more than 70 % of the subjects belonging to the same group. We collected all the clusters satisfying this condition over the 1,000 trials, we computed the centroid (i.e., the mean 10-scores profile) for each cluster, and finally, we calculated the average centroids representing the three groups and their standard deviation.

Statistical analysis of SRS data

A one-way ANOVA was computed for each of SRS Scales: Social Awareness, Social Cognition, Social Communication, Social Motivation, Restricted Interests and Repetitive Behavior, using Group as factor (three levels: TD, Siblings, ASD). If significant main effect was found, post hoc analysis was conducted with a Bonferroni correction for multiple comparisons.

Results

A preliminary analysis, performed on FSIQ values, was aimed to identify the outliers within each population. The mean value of FSIQ and its standard deviation were computed for ASD, Siblings, and TD groups. Participants whose values laid outside the mean ± three standard deviations of their group were discarded from subsequent evaluation. No outliers were found for both Siblings and ASD, while one TD subject was excluded. The final numbers of tested children were 31 ASD (23 males and 8 females, mean age 9.03 years; SD 2.61 years), 21 Siblings (12 males and 9 females, mean age 9.86 years; SD 2.66 years), and 42 TD (15 males and 27 females, mean age 7.88 years; SD 1.73 years). Table 1 reports the participants' characteristics for each investigated group of children.

To assess the homogeneity of the studied sample, we conducted a two-way ANOVA on the Age of the children with Group and Sex as factors. The results indicated a significant Group effect [$F(2,88) = 5.70$, $p < 0.01$]. Post hoc analysis indicated that Siblings group was older than TD ($p = 0.004$). No further significant difference was found. In addition, no significant Sex main effect or Group*Sex interaction was detected.

A second ANOVA compared the FSIQ of the three populations. The ANOVA [$F(2, 88) = 61.89$, $p < 0.0001$] and relative post hoc analysis showed a significant difference between ASD and the other two groups. More specifically, TD and Siblings had FSIQ higher than ASD (all post hoc comparisons revealed a p value lower than 0.0001). Siblings and TD groups did not differ on FSIQ score. No significant effect was found relative to the Sex factor.

In a further two-way ANOVA (with Group and Sex as factors), the VIQ scores of the three groups were analyzed. VIQ scores showed a significant Group effect [$F(2, 88) = 65.78$, $p < 0.0001$]. The results are shown in Fig. 1a.

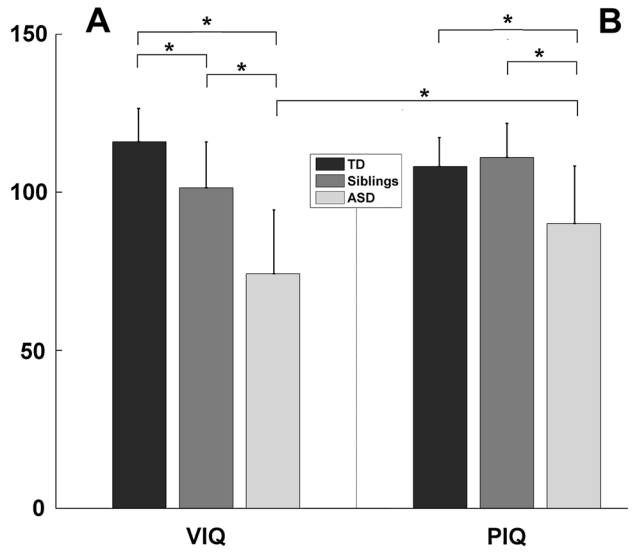

Fig. 1 VIQ and PIQ values. The three groups are reported: typically developing children (TD), Siblings and children with autism (ASD). The *y*-axis indicates the VIQ (**a**) and PIQ (**b**), normalized according to the Italian normative sample, whose mean score is set to 100 and standard deviation to 15. The *error bars* indicate the standard deviation for each group and subscale. The Scale*Group interaction was assessed by a repeated measurements ANOVA ($p < 0.001$). *Asterisks* indicate the significant post hoc comparisons. Note that only ASD children showed a significant difference between verbal and performance scores

Post hoc analysis revealed the existence of significant VIQ differences across all examined groups (all p values were lower than 0.0001). In particular, TD exhibited the highest VIQ value (mean 116), followed by Siblings (mean 101), and finally, by ASD (mean 71). Sex main effect and Group*Sex interaction resulted to be not significant.

A two-way ANOVA with the same factors as for VIQ scores was conducted on PIQ scores. This analysis was also significant [$F(2,88) = 18.64$, $p < 0.0001$, see Fig. 1b]. In the Performance Scale, no significant difference was found between TD (mean 108) and Siblings (mean 111), while ASD group was characterized by significantly lower scores (mean 90, $p < 0.0001$ vs. other two groups). No significant Group*Sex interaction was found.

IQ profile

A repeated measurement ANOVA was then conducted on VIQ and PIQ values to assess the IQ profile within each investigated population. Group (three levels) and Sex (two levels) were the between-subjects factors, and Scale (two levels: VIQ/PIQ) was the within-subjects factor. Both Group [$F(2,88) = 60.18$, $p < 0.0001$] and Scale [$F(1,88) = 10.79$, $p < 0.005$] main effect were found to be significant, as well as the Group*Scale interaction [$F(2,88) = 18.96$, $p < 0.0001$]. Post hoc analysis within each population revealed that only ASD children were characterized by a significant difference between verbal and performance scores ($p < 0.0001$, see Fig. 1). No interaction involving Sex factor was found to be significant. Note that only ASD group exhibited an IQ profile with performance scores exceeding the verbal ones for more than 15 points (mean difference, −16). No clinically relevant difference between VIQ and PIQ scores existed in TD and Siblings populations. However, while this difference was positive for TD, it was, as in ASD group, negative (−10) for Siblings.

In summary, TD group individuals appear to be balanced in their IQ profile, even if with a slight preference for verbal abilities. On the contrary, a strong predominance of performance abilities is evident in ASD group. Interestingly, although not significant, a similar IQ profile was observed in Siblings group that showed a predominance of performance over verbal abilities.

Cognitive profile

Verbal Scale

Figure 2a shows the absolute scores for each subtest of the Verbal Scale. The normality range is reported, with the horizontal solid thick line representing the mean normalized score (10) and the dotted thin lines the one standard deviation confidence interval (3) according to the Italian WISC-III standardization (Orsini and Picone 2006). TD and Siblings groups showed values within normality range for all subtests. In contrast, children with ASD showed lower values relative to the other two groups, particularly in Arithmetic (AR), Vocabulary (VO), and Comprehension (CM) subtests, whose scores laid outside the normality range.

The normalization of each subject values allowed us to obtain a cognitive profile that describes the individual relative abilities, regardless their global verbal and performance scores. Data for each population in the same subtests were statistically assessed by means of a one-sample t test. The results for verbal subtests are shown in Fig. 3a. The most interesting result concerns the CM subtest (white bars). While there is a large and significant weakness in CM for Siblings ($p = 0.0004$, power = 0.95) and ASD children ($p < 0.0001$, power = 1), this subtest represents strength for TD children ($p < 0.0001$, power = 1). In addition, while TD group has near-to-zero score for the SM subtest (dark gray bar), both ASD ($p = 0.0002$, power = 1) and Siblings ($p < 0.0001$, power = 1) exhibit high scores in it.

It must be noted that this analysis does not compare the populations in terms of their absolute subtest scores, i.e., a greater score of population A versus population B does not imply that A performs better than B in a given subtest. What these data indicate is which cognitive abilities are more developed, within a population, relative to others.

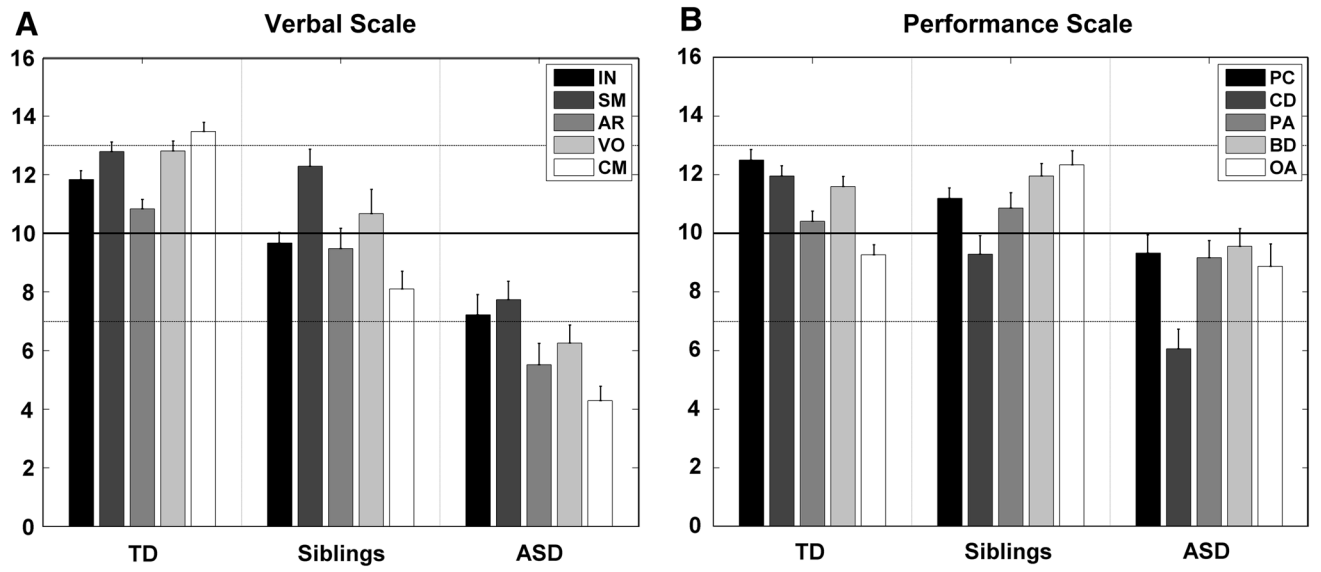

Fig. 2 WISC-III absolute scores. All subtests relative to WISC-III are reported. **a** The absolute scores relative to the Verbal Scale, **b** relative to the Performance Scale. The *y*-axis indicates the scores normalized according to the Italian normative sample, whose mean (10) is indicated by a *black thick line*. *Dotted lines* indicate the 1 SD confidence interval (±3). The *error bars* indicate the standard deviation for each subtest and population

The results relative to CM clearly indicate this as the key weakness for ASD children. To evaluate the distribution of this variable within the ASD population and across the degrees of symptoms severity, the correlation between CM and age on one side, and between CM and ADOS total scores on the other side was computed (see Fig. 3c). Both resulted to be not significant ($p = 0.74$ and $p = 0.43$, respectively), indicating that this weakness is homogeneously distributed across age and symptoms severity in ASD children.

Performance Scale

Figure 2b reports the absolute scores for each subtests in the Performance Scale. ASD scores result to be largely within the normal clinical range (>7) with the exception of coding (CD) subtest (dark gray bar).

In the Performance Scale, the analysis of normalized profiles identified a specific subtest (CD) as maximally different between TD and the other two populations (Fig. 3b). The CD scores represented the significant and major weakness for Siblings ($p = 0.0019$, power $= 0.84$) and ASD ($p < 0.0001$, power $= 1$). In the latter population, values were so low to counterbalance all other subtests score, whose average resulted therefore to be positive. On the contrary, TD participants exhibited a positive and significant value in this subtest ($p = 0.0098$, power $= 0.56$).

The correlations of CD subtest with age and ADOS total scores were assessed as for the CM subtest in the Verbal Scale (see Fig. 3d). Both resulted to be not significant ($p = 0.36$ and $p = 0.44$, respectively), indicating that this weakness does not vary with the age and the symptoms severity, but rather that this is a marker of the relative cognitive profile in ASD children.

Clustering analysis

The specificity of the different cognitive profile for each group was also assessed using a clustering analysis. For each computed cluster, a centroid was defined as the mean relative profile of all clustered participants. Subsequently, the average centroid for all clusters representative of a given population was calculated and reported in Fig. 4. The centroid for the TD group resulted to be clearly segregated from the ones relative to Siblings and ASD children. In particular, the identification of the subtests carrying the most of this difference confirmed the results of the cognitive profile analysis. Scores relative to subtests CM, CD, and OA resulted to be opposite for TD population relative to the other two groups.

To quantify the reliability of these results, we evaluated for each population how many runs returned a representative cluster, i.e., how often (at least) 70 % of the elements of a single cluster belonged to the same population. We found a cluster representing the TD population in the vast majority of cases (94.7 %), while Siblings and ASD populations exhibited lower values (10.9 and 55.2 %, respectively), indicating that these participants were more spread across the clusters. For this reason, we conducted a further analysis on all the runs failing to identify a cluster representative of Siblings; we evaluated which populations are mainly intermixed with them, taking into account the single cluster

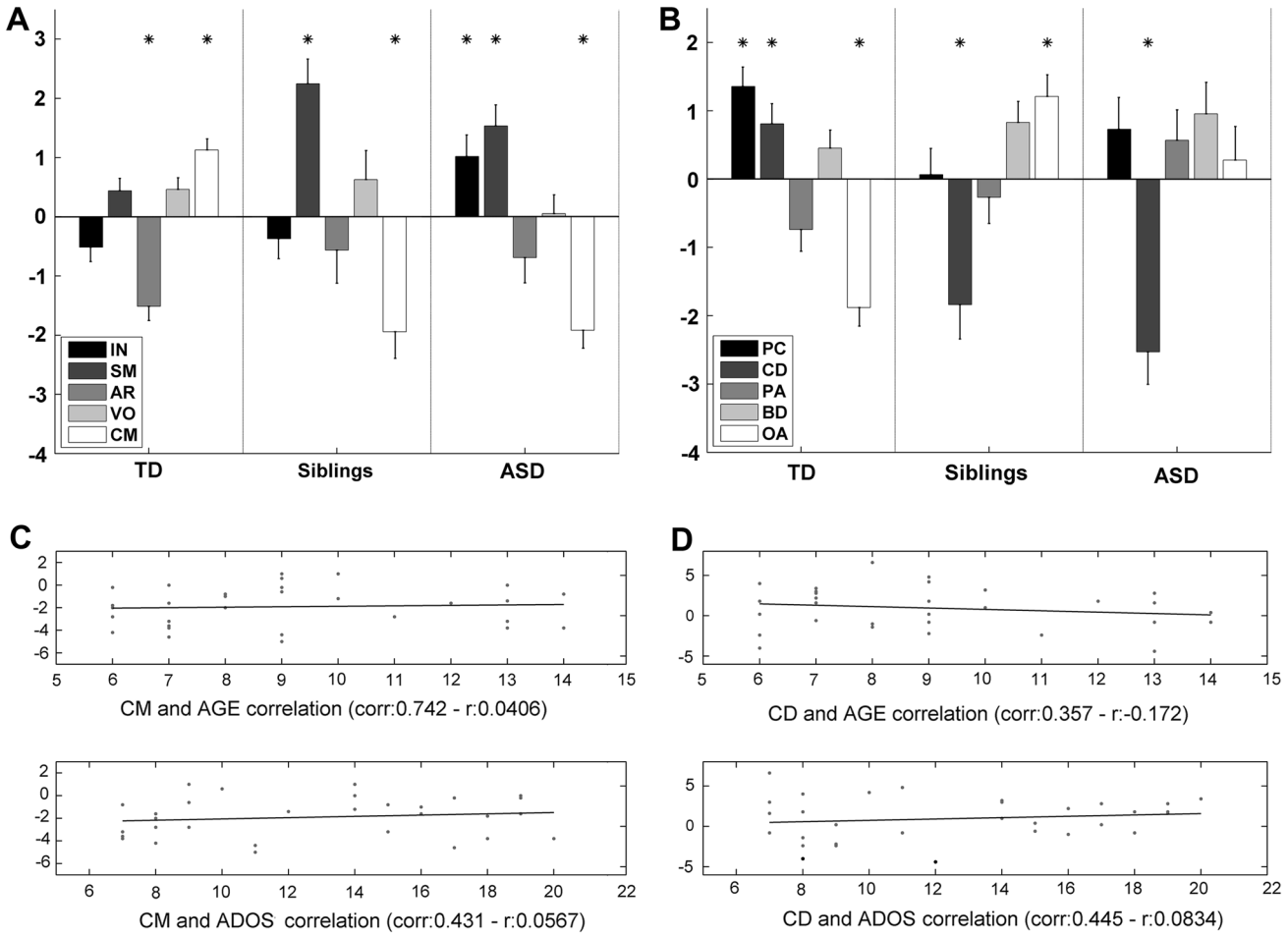

Fig. 3 WISC-III normalized scores. All subtests relative to WISC-III are reported. The *y*-axis indicates normalized scores for each subject relative to the average of all subtests belonging to the same scale. **a** Reports values for the Verbal Scale, **b** the values relative to the Performance Scale. Data from the same subtests and population were statistically assessed by means of a one-sample *t* test. *Asterisks* indicate whether the statistical significance is present ($p < 0.01$). Comprehension (CM) and Coding (CD) subtests were identified as maximally different between TD on one side, and ASD and Siblings on the other. The correlations between CM scores and either age and ADOS total score within ASD population are reported in **c**. The same correlations for CD scores are reported in **d**

including most of the Siblings subjects. Results indicated that Siblings and ASD subjects (48.09 and 49.66 %, respectively) usually fall within the same clusters, while they have little or no overlap with TD children (2.25 %). These data indicate that, once discarded the global cognitive functioning and isolated only its internal pattern, Siblings of autistic children exhibit a pattern common to their affected relatives, while they result to be clearly different from TD group. In addition, they indicate that this similarity is not limited to the scores relative to two subtests, but that the whole relative cognitive profile co-segregates Siblings and ASD children.

Social Responsiveness Scale (SRS)

The SRS total scores were clearly different for TD and Siblings on one side and for ASD on the other side. The mean values for TD and Siblings were 26.98 and 21.00, respectively, while for ASD, it was equal to 98.53. The main effect of Group resulted to be highly significant [$F(2,71) = 88.15$, $p < 0.0001$]. Post hoc analysis indicated that no statistical difference existed between TD and Siblings, and in contrast, both these groups differed from children with ASD ($p < 0.0001$). Each SRS subscale showed a pattern virtually identical to that relative to SRS total scores.

Discussion

In the present study, we assessed the *cognitive profile*, i.e., the relationship among all subtests of the WISC Verbal and Performance Scales, of ASD children and their unaffected siblings. A group of TD children was also tested. ASD and Siblings presented a surprising similarity in terms of their

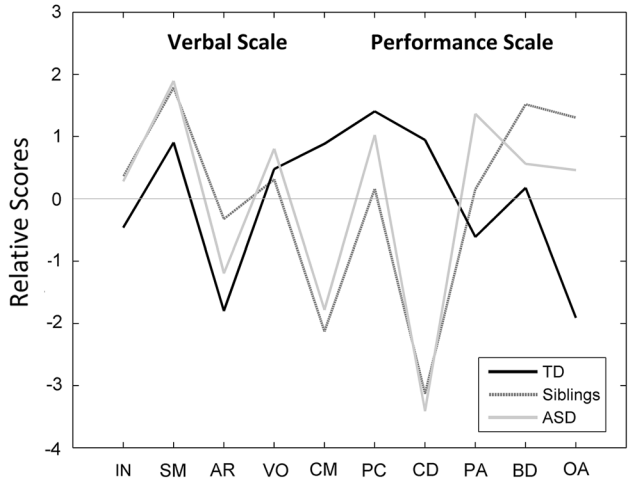

Fig. 4 Clustering analysis. The profiles of three groups are reported: typically developing children (TD), Siblings and children with autism (ASD). Each profile was computed as the average centroid of all the clusters representative for a given population, i.e., all clusters whose at least 70 % of elements belonged to the same population. Note that CM and CD subtests carry the most of the difference between TD group and all other populations

cognitive profile, sharing the same weaknesses in both verbal and performance subscales. In contrast, TD children exhibited a radically different profile. The same subtests that represented the major weaknesses in ASD and Siblings resulted to be the strengths for the control group.

A large previous literature showed that lower scores in VIQ relative to PIQ characterize the IQ profile of children with autism (see "Introduction"). Furthermore, studies focusing on the cognitive profile of autistic children highlighted that Comprehension (CM) subtest in the Verbal Scale and Coding (CD) subtest in the Performance Scale were the most impaired items (Lincoln et al. 1988; Venter et al. 1992; Happé 1994; for a review see Siegel et al. 1996). The present data fully confirm these findings.

At a first glance, looking at the absolute scores, Siblings do not show any clear difference relative to TD group. They present FSIQ scores matching the TD ones and no clinically significant unbalance between verbal and performance abilities. In contrast, Siblings appear to be radically different from ASD children in terms of FSIQ, VIQ, and PIQ, whose scores are much lower for ASD group.

If one examines, however, the pattern of weaknesses and strengths within these scales, the surprising finding is that the cognitive profiles of Siblings and ASD present a marked similarity, regardless of their absolute values. First as far as IQ profile is concerned, in line with the scores of their affected relatives, Siblings show a predominance of performance over verbal abilities. It must be noted, however, that unlike in ASD children, this difference does not reach statistical significance. Second, as far as the *cognitive profile* is concerned, data revealed that both ASD and Siblings present their main weaknesses in Comprehension and Coding.

One may argue that this resemblance is marginal, because is limited to only few subtests. To address this possible criticism, we run a clustering analysis, giving as input the entire 10-scores profile of all subjects with no information about the group each subject belonged to. The data showed that, in terms of relative cognitive profile, Siblings are clearly segregated from TD children and highly overlapped with their affected relatives.

The similarity between the cognitive profile of ASD children and their Siblings raises an interesting question. Is this cognitive profile determined by the symptoms that characterize ASD or is it *concomitant* to them? The present data suggest that is not the disease that determines this profile. In fact, both the results of SRS and the behavioral profile reported by parents highlighted the absence of any core symptoms of ASD for Siblings population. Thus, it appears plausible that the specific cognitive profile, we described in the present study, represents a cognitive endophenotype of ASD.

There is a large literature showing that endophenotypes of psychiatric syndromes are under the control of fewer genes than a given syndrome (Kendler and Neale 2010). In this view, one should expect that also in ASD, endophenotypes should be independent of the severity of the symptoms and of other variables tightly linked to the disorder. The absence of significant correlations between the scores of CM and CD subtests and ADOS total scores supports this view. It demonstrates that the specific cognitive pattern we found in ASD children and their siblings is spread over the entire ASD group, regardless the severity of the syndrome. In line with this conclusion is also the lack of significant correlations between CM and CD scores and children age.

According to DSM V (APA 2013), autistic spectrum disorder is considered as a "family of dimensional phenotypes." As genetic factors contributing to an endophenotype are more easily identifiable relative to those explaining the full clinical profile, research on the identification of genetically meaningful endophenotype could provide an important insight into genetics of autism. An interesting hypothesis is that the expression of autism could depend on multiple genetic independent factors, each with a small effect size. The genetic expression of the cognitive profile with the specific weaknesses we found in the siblings of ASD is obviously not sufficient for determining the occurrence of the disorder. However, it is plausible that the association of the cognitive endophenotype we described here with other concomitant genetic variants may lead to the full-fledged expression of autism which, in the absence of the former, could not determine the full expression of the disease.

Acknowledgments VG, PA and CC were supported by ERC Grant Cogsystem to GR, contract no. 250013. We thank Dr. Fabio Sambataro and Sonia Boria for critical reading and for their remarks on previous versions of the manuscript. A special thanks to the staff of the Pediatric Neuropsychiatry of Empoli, of the rehabilitation center for autism "Centro Mai Soli" in Genova, of the Institute of Rehabilitation "Village Eugenio Litta," Grottaferrata, Roma, and of the Autism Center of Parma for their invaluable collaboration in data collection. We also thank the staff and families of IV Circolo "Risorgimento - San Berardo" primary school in Teramo for providing the control group. Last but not least, thanks to all the children and their families for the availability and patience.

References

Allen MH, Lincoln AJ, Kaufman AS (1991) Sequential and simultaneous processing abilities of high-functioning autistic and language-impaired children. J Autism Dev Disord 21:483–502

Almasy L, Blangero J (2001) Endophenotypes as quantitative risk factors for psychiatric disease: rationale and study design. Am J Med Genet 105:42–44

American Psychiatric Association (2000) Diagnostic and statistical manual of mental disorders, 4th edn., text revised. American Psychiatric Association, Washington, DC

American Psychiatric Association (2013) Diagnostic and statistical manual of mental disorders, 5th edn. American Psychiatric Publishing, Arlington

Anderberg MR (1973) Cluster analysis for applications. Academic Press, New York

Ankenman K, Elgin J, Sullivan K, Vincent L, Bernier R (2014) Nonverbal and verbal cognitive discrepancy profiles in autism spectrum disorders: influence of age and gender. Am J Intellect Dev Disabil 119:84–99

Asarnow RF, Tanguay PE, Bott L, Freeman BJ (1987) Patterns of intellectual functioning in non-retarded autistic and schizophrenic children. J Child Psychol Psychiatry 28:273–280

August GJ, Stewart MA, Tsai L (1981) The incidence of cognitive disabilities in the siblings of autistic children. Br J Psychiatry 138:416–422

Buitelaar JK, van der Wees M, Swaab-Barneveld H, van der Gaag RJ (1999) Theory of mind and emotion-recognition functioning in autistic spectrum disorders and in psychiatric control and normal children. Dev Psychopathol 11:39–58

Caron MJ, Mottron L, Berthiaume C, Dawson M (2006) Cognitive mechanisms specificity and neural underpinnings of visuospatial peaks in autism. Brain 129:1789–1802

Castelli F (2005) Understanding emotions from standardized facial expressions in autism and normal development. Autism Int J Res Pract 9:428–449

Charman T, Jones CRG, Pickles A, Simonoff E, Baird G, Happé F (2011) Defining the cognitive phenotype of autism. Brain Res 1380:10–21

Constantino JN, Gruber CP (2005) Social Responsiveness Scale (SRS). Western Psychological Services, Los Angeles

Constantino JN, Frazier TW et al (2013) Commentary: The observed association between autistic severity measured by the social responsiveness scale (SRS) and general psychopathology-a response to Hus et al (2013). J Child Psychol Psychiatry 54:695–697

Delorme R, Gousse V, Roy I, Trandafir A, Mathieu F, Mouren-Simeoni MC, Betancur C, Leboyer M (2007) Shared executive dysfunctions in unaffected relatives of patients with autism and obsessive-compulsive disorder. Eur Psychiatry 22:32–38

Dennis M, Lockyer L, Lazenby AL, Donnelly RE, Wilkinson M, Schoonheyt W (1999) Intelligence patterns among children with high-functioning autism phenylketonuria and childhood head injury. J Autism Dev Disord 29:5–17

Ehlers S, Nydén A, Gillberg C, Sandberg AD, Dahlgren SO, Hjelmquist E, Odén A (1997) Asperger syndrome autism and attention disorders: a comparative study of the cognitive profiles of 120 children. J Child Psychol Psychiatry 38:207–217

Folstein SE, Santangelo SL, Gilman SE, Piven J, Landa R, Lainhart J, Hein J, Wzorek M (1999) Predictors of cognitive test patterns in autism families. J Child Psychol Psychiatry 40:1117–1128

Fombonne E, Bolton P, Prior J, Jordan H, Rutter M (1997) A family study of autism: cognitive patterns and levels in parents and siblings. J Child Psychol Psychiatry 38:667–683

Freeman BJ, Ritvo ER, Needleman R, Yokota A (1985) The stability of cognitive and linguistic parameters in autism: a five-year prospective study. J Am Acad Child Adolesc Psychiatry 24:459–464

Freeman BJ, Ritvo ER, Mason-Brothers A, Pingree C, Yokota A, Jenson WR, McMahon WM, Petersen PB, Mo A, Schroth P (1989) Psychometric assessment of first-degree relatives of 62 autistic probands in Utah. Am J Psychiatry 146:361–364

Girardot AM, De Martino S, Chatel C, Da Fonseca D, Rey V, Poinso F (2012) Cognitive profiles in pervasive developmental disorders. Encephale 38:488–495

Gottesman II, Gould TD (2003) The endophenotype concept in psychiatry: etymology and strategic intentions. Am J Psychiatry 160:636–645

Happé FG (1994) Wechsler IQ profile and theory of mind in autism: a research note. J Child Psychol Psychiatry 35:1461–1471

Hughes C, Plumet MH, Leboyer M (1999) Towards a cognitive phenotype for autism: increased prevalence of executive dysfunction and superior spatial span amongst siblings of children with autism. J Child Psychol Psychiatry 40:705–718

Hus V, Bishop S, Gotham K, Huerta M, Lord C (2013a) Commentary: Advancing measurement of ASD severity and social competence: a reply to Constantino and Frazier 2013. J Child Psychol Psychiatry 54:698–700

Hus V, Bishop S, Gotham K, Huerta M, Lord C (2013b) Factors influencing scores on the social responsiveness scale. J Child Psychol Psychiatry 54:216–224

Kaland N, Mortensen EL, Smith L (2007) Disembedding performance in children and adolescents with Asperger syndrome or high-functioning autism. Autism 11:81–92

Kawakubo Y, Kuwabara H, Watanabe K, Minowa M, Someya T, Minowa I, Kono T, Nishida H, Sugiyama T, Kato N, Kasai K (2009) Impaired prefrontal hemodynamic maturation in autism and unaffected siblings. PLoS ONE 4:e6881

Kendler KS, Neale MC (2010) Endophenotype: a conceptual analysis. Mol Psychiatry 15:789–797

Leboyer M, Plumet MH, Goldblum MC, Perez-Diaz F, Marchaland C (1995) Verbal versus visuospatial abilities in relatives of autistic females. Dev Neuropsychol 11:139–155

Lincoln AJ, Courchesne E, Kilman BA, Elmasian R, Allen M (1988) A study of intellectual abilities in high-functioning people with autism. J Autism Dev Disord 18:505–524

Lockyer L, Rutter M (1970) A five- to fifteen-year follow-up study of infantile psychosis. IV. Patterns of cognitive ability. Br J Soc Clin Psychol 9:152–163

Lord C, Rutter M, Goode S, Heemsbergen J, Jordan H, Mawhood L, Schopler E (1989) Autism diagnostic observation schedule: a standardized observation of communicative and social behavior. J Autism Dev Disord 19:185–212

Losh M, Adolphs R, Poe MD, Couture S, Penn D, Baranek GT, Piven J (2009) Neuropsychological profile of autism and the broad autism phenotype. Arch Gen Psychiatry 66:518–526

Mayes SD, Calhoun SL (2003) Analysis of WISC-III, Stanford-Binet: IV and academic achievement test scores in children with autism. J Autism Dev Disord 33:329–341

Minton J, Campbell M, Green WH, Jennings S, Samit C (1982) Cognitive assessment of siblings of autistic children. J Am Acad Child Adolesc Psychiatry 21:256–261

Narita T, Koga Y (1987) Neuropsychological assessment of childhood autism. Adv Biol Psychiatry 16:156–170

Neves MD, Tremeau F, Nicolato R, Lauar H, Romano-Silva MA, Correa H (2011) Facial emotion recognition deficits in relatives of children with autism are not associated with 5HTTLPR. Revista brasileira de psiquiatria 33:261–267

Oerlemans AM, van der Meer JMJ, van Steijn DJ, de Ruiter SW, de Bruijn YGE, de Sonneville LMJ, Buitelaar JK, Rommelse NNJ (2013) Recognition of facial emotion and affective prosody in children with ASD (+ADHD) and their unaffected siblings. Eur Child Adolesc Psychiatry. doi:10.1007/s00787-013-0446-2

Ohta M (1987) Cognitive disorders of infantile autism: a study employing the WISC spatial relationship conceptualization and gesture imitations. J Autism Dev Disord 17:45–62

Orsini L, Picone S (2006) Weschsler Intelligence Scale for Children—III Edizione Italiana Giunti OS, Firenze

Ozonoff S, Pennington BF, Rogers SJ (1991) Executive function deficits in high-functioning autistic individuals: relationship to theory of mind. J Child Psychol Psychiatry 32:1081–1105

Ozonoff S, Rogers SJ, Farnham JM, Pennington BF (1993) Can standard measures identify subclinical markers of autism? J Autism Dev Disord 23:429–441

Pilowsky T, Yirmiya N, Gross-Tsur V, Shalev RS (2007) Neuropsychological functioning of siblings of children with autism, siblings of children with developmental language delay and siblings of children with mental retardation of unknown of genetic etiology. J Autism Dev Disord 37:537–552

Piven J, Palmer P, Jacobi D, Childress D, Arndt S (1997) Broader autism phenotype: evidence from a family history study of multiple-incidence autism families. Am J Psychiatry 154:185–190

Ropar D, Mitchell P (2001) Susceptibility to illusions and performance on visuospatial tasks in individuals with autism. J Child Psychol Psychiatry 42:539–549

Schneider SG, Asarnow RF (1987) A comparison of cognitive/neuropsychological impairments of non retarded autistic and schizophrenic children. J Abnorm Child Psychol 15:29–45

Shah A, Frith U (1993) Why do autistic individuals show superior performance on the block design task? J Child Psychol Psychiatry 34:1351–1364

Siegel DJ, Minshew NJ, Goldstein G (1996) Wechsler IQ profiles in diagnosis of high-functioning autism. J Autism Dev Disord 26:389–406

Szatmari P, Tuff L, Finlayson MA, Bartolucci G (1990) Asperger's syndrome and autism: neurocognitive aspects. J Am Acad Child Adolesc Psychiatry 29:130–136

Szatmari P, Jones MB, Tuff L, Bartolucci G, Fisman F, Mahoney W (1993) Lack of cognitive impairment in first-degree relatives of children with pervasive developmental disorder. J Am Acad Child Adolesc Psychiatry 32:1264–1273

Venter A, Lord C, Schopler E (1992) A follow-up study of high-functioning autistic children. J Child Psychol Psychiatry 33:489–507

Waldman ID (2005) Statistical approaches to complex phenotypes: evaluating neuropsychological endophenotypes for attention-deficit/hyperactivity disorder. Biol Psychiatry 57:1347–1356

Wechsler D (1974) Manual for the Wechsler Intelligence Scale for Children—revised. Psychological Corporation, New York

Wechsler D (1991) Wechsler Intelligence Scale for Children—third edition manual. Psychological Corporation, New York

Wechsler D (2003) WISC-IV technical and interpretative manual. Psychological Corporation, San Antonio