

Identifying neurocognitive phenotypes in autism

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Autism is a complex disorder that is heterogeneous both in its phenotypic expression and its etiology. The search for genes associated with autism and the neurobiological mechanisms that underlie its behavioural symptoms has been hampered by this heterogeneity. Recent studies indicate that within autism, there may be distinct subgroups that can be defined based on differences in neurocognitive profiles. This paper presents evidence for two kinds of subtypes in autism that are defined on the basis of language profiles and on the basis of cognitive profiles. The implications for genetic and neurobiological studies of these subgroups are discussed, with special reference to evidence relating these cognitive phenotypes to volumetric studies of brain size and organization in autism.

Keywords: autism; phenotype; cognitive profile; specific language impairment; language; macrocephaly

1. INTRODUCTION

Autism is a neurodevelopmental disorder that is defined on the basis of behavioural symptoms. Among the major goals of research in this field are to find the underlying causes and to develop novel treatments that will alleviate the severe and debilitating effects of autism on children and their families. These goals can only be achieved when the disorder can be objectively and reliably diagnosed, and has a clearly defined phenotype. Over the past decade international consensus has been reached on the clinical diagnostic criteria for autism and other ASDs within ICD-10 and DSM-IV (World Health Organization 1993; American Psychiatric Association 1994). These criteria have been implemented in the ADI-R (Lord *et al.* 1994) and the ADOS (Lord *et al.* 1999), which are now widely used to obtain reliable and valid classification of individuals with ASD for research purposes.

The introduction of these diagnostic criteria and gold-standard instruments has led to a significant increase in studies investigating the etiology of autism. Genetic studies have shown the greatest promise in this area, and twin and family studies indicate that the heritability estimates for autism are over 90%, far exceeding other psychiatric disorders (Bailey *et al.* 1995). Evidence indicates that anywhere from 2 to 10 interacting genes are involved (Pickles *et al.* 1995; Santangelo & Folstein 1999) and numerous studies using different methodological strategies have been launched to find these genes by using advances in human genome research and molecular biology (see Lamb *et al.* (2000), Rutter (2000) and Folstein & Rosen-Sheidley (2001) for recent reviews). Some cases of autism are associated with other medical conditions, including known genetic disorders (e.g. fragile X syndrome). However, recent estimates indicate that these cases account for only

10–15% of all cases of autism (Rutter *et al.* 1994; Barton & Volkmar 1998) and they are generally excluded from genetic studies of ‘idiopathic’ autism. Despite the advances that have been made, and reports of some positive findings from both linkage and association genetic studies, thus far not a single susceptibility gene for autism has been identified. The current view is that each locus identified in these studies contains genes with only small or moderate effects on the etiology of autism. These small effect sizes make the identification of specific genes significantly more difficult, especially given the relative rarity of the disorder and the fact that it involves both phenotypic and genetic heterogeneity.

Numerous researchers have argued that new approaches, which go beyond the standard methods, will be needed for real advances to be made in finding genes for autism over the next few years (Szatmari 1999; Risch *et al.* 1999; Rutter 2000). One way to enhance the possibility of finding a larger genetic effect size is to reduce the phenotypic variability in the sample in ways that go beyond simply excluding non-idiopathic cases (cf. Miles & Hillman 2000). By constraining the phenotype, one might expect a more homogeneous genetic etiology (Leboyer *et al.* 1998; but cf. Le Couteur *et al.* 1996). There are several methods available for narrowing down the phenotype of autism. One involves identifying *subtypes* within autism (Szatmari 1999). Several studies have used this approach by looking for meaningful groupings within the diagnostic classifications for ASD (e.g. Asperger syndrome, pervasive developmental disorder). With the exception of Rett syndrome, now known to be caused by mutations in a single gene (Amir *et al.* 1999), these studies have yielded mixed results and have not had a significant impact on genetic research (e.g. Mahoney *et al.* 1998; Prior *et al.* 1998).

In this paper, we report on a different approach for finding subtypes within autism that may be useful for genetic studies, one focusing on aspects of the phenotype that are not part of the core defining features of the disorder. The particular strategy we have taken is to investigate cognitive

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characteristics that are found in some, but not all, children with autism, thus providing more homogeneous subtypes that are defined along dimensions that could potentially be linked to specific patterns of neuropathology. We describe our research on the two most promising autism subtypes in autism that we have investigated thus far:

- (i) distinguishing between children with normal language abilities from those who are language impaired, and
- (ii) distinguishing between children with discrepantly high NV intelligence scores from those who do not show this cognitive profile on standardized psychometric tests.

2. LANGUAGE ABILITIES IN AUTISM

Deficits in language and communication are among the defining symptoms of autism (American Psychiatric Association 1994), although Kanner (1943) did not consider these features to be central to what distinguished autism as a unique syndrome. Most studies have focused on identifying deficits in the language domain that are universally and uniquely found in autism, and there is general agreement that pragmatic and discourse skills represent core areas of dysfunction in this disorder (for reviews, see Lord & Paul 1997, Wilkinson 1998 and Tager-Flusberg 1999). Relatively little research in recent years has investigated other aspects of language in autism, yet it is clear that most children with autism have language deficits that go beyond impaired pragmatic ability. For example, most children with autism show significant delays in acquiring language, and about half remain essentially NV (Bailey *et al.* 1996). Many of those children who acquire some spontaneous use of language show deficits in vocabulary and the acquisition of complex syntax and morphology (e.g. Bartak *et al.* 1975). Thus, in autism there are often problems in both structural and pragmatic aspects of language (Rapin & Dunn 1997; Ballaban-Gil *et al.* 1997). However, the former are more variable, are not unique to autism and are not necessarily correlated with the degree of severity of core autism features or level of cognitive functioning.

We conducted two studies designed to investigate language impairments in autism with particular interest in exploring the variability in structural aspects of language. We followed up these behavioural studies with an investigation of structural brain patterns in children with autism, using MRI to detect regional brain volume differences that might be related to the language impairments that were found in the behavioural studies.

(a) *Study Ia: language profiles in autism*

A large sample of 89 children with autism (9 girls and 80 boys), between the ages of 4 and 14, participated in this study (Kjelgaard & Tager-Flusberg 2001). They were selected on the basis of having at least some language, defined as the ability to use some two-word utterances, and were diagnosed using the DSM-IV criteria on the basis of algorithm scores on the ADI-R and ADOS, and confirmed by an expert clinician. The research form of the ADI-R (Lord *et al.* 1994) and the ADOS (Lord *et al.* 2000) were administered by specially trained personnel

who demonstrated reliability in scoring with the authors of the instruments and on-site trainers. The IQ of each child was assessed with the DAS (Elliott 1990). For this sample, the mean IQ was 68 and scores ranged from 25 (floor) to 141.

A battery of standardized tests was individually administered to the children to measure their phonological, lexical and higher-order semantic and grammatical language abilities. Phonological skills were assessed using the Goldman-Fristoe Test of Articulation (Goldman & Fristoe 1986) that measures the accuracy of productive phonology for the consonant sounds of English, and the RNW test taken from the Developmental Neurophysiological Assessment Battery (Korkman *et al.* 1998). This latter test measures the ability to analyse and reproduce phonological knowledge by asking the child to repeat nonsense words that are presented on an audiotape. Lexical knowledge was assessed using the PPVT (Dunn & Dunn 1997), a widely used measure of lexical comprehension, and the EVT (Williams 1997), a measure of productive vocabulary. Higher-order semantic and grammatical skills were assessed using the CELF (Wiig *et al.* 1992; Semel *et al.* 1995). This is an omnibus test comprised of six subtests designed to measure receptive and expressive grammatical morphology, syntax, semantics and working memory for language. For each test, the child's standard score was computed, based on a mean of 100 and a standard deviation of 15 points.

Owing to the wide variability in the language skills of the children, in many cases not all the tests were completed. We were able to obtain standard scores on the Goldman-Fristoe test, the PPVT and EVT for almost all the children in the sample, but only about half could be scored on the CELF and the RNW test. In general, regardless of age, those children with higher IQ scores were more likely to complete these more complex tests, which have considerable attentional, working memory and other test-related factors associated with them.

Our primary interest was in exploring differences in language profiles across the standardized tests in children with relatively good language skills compared with those with clear impairments. We present here the data based on those children who were able to complete all the language tests. Most of the 44 children in this group had NV IQ scores in the normal range. This group was divided into three subtypes based on their total CELF standard scores. The participants in the *normal language subtype* group had CELF scores 85 or higher (within 1 s.d. of the mean), and included 10 children, or 23% of the children. The participants in the *borderline language subtype* group had CELF scores between 70 and 84; more than 1 s.d. below the mean but less than 2. There were 13 children in the borderline subtype, representing 30% of the sample. The participants in the *impaired-language subtype* group had CELF scores below 70, more than 2 s.d. below the mean. There were 21 children in this subtype; 47% of the group who were able to complete all the standardized language tests.

Figure 1 presents the profile of scores across the language tests for the participants within each of the subtypes. The PPVT and EVT scores were combined since they were highly correlated with one another and the tests were normed on the same sample. At a group level, the children

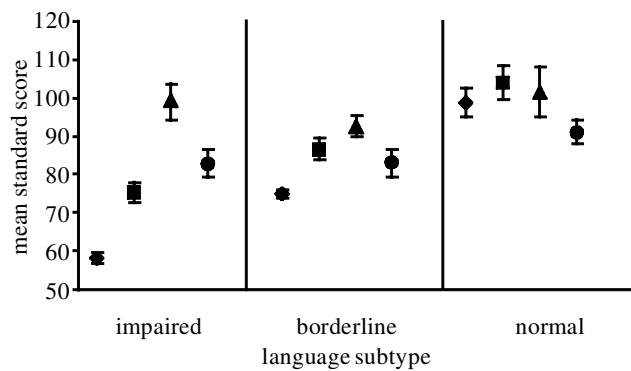


Figure 1. The profile of performance across the standardized test by the impaired, borderline and normal language subtype groups. Diamonds, CELF total; squares, PPVT + EVT; triangles, Goldman-Fristoe test; circles, RNW.

in the normal language subtype had scores on all the language measures that were well within the normal range, representing a relatively flat profile. These children had normal phonological, lexical, morphological and syntactic skills, as measured by the standardized tests used in this study. By contrast, the children in the borderline and impaired subtypes had deficits in higher-order syntax and semantics, vocabulary and the ability to represent and reproduce novel phonological sequences, as measured by the RNW test. Differences between the subtypes were statistically significant for vocabulary scores ($F_{2,41} = 19.45$, $p < 0.0001$), but did not reach significance on the RNW test ($F_{2,28} = 1.77$, n.s.). The impaired children did not have deficits in basic articulation skills, as can be seen by their scores on the Goldman-Fristoe test, which fell within the normal range; this was confirmed in a one-way ANOVA showing no differences among the subtypes on this test ($F_{2,39} = 0.82$, n.s.).

At the individual level, there was good consistency in meeting the subtype profiles for the children in the normal and impaired groups. Within the normal subtype eight of the ten children fitted the profile of scores within the normal range across all the language tests; the remaining two children fell one point below the normal range on RNW. Of the 21 children in the impaired subtype, 14 (two-thirds) met the profile with scores more than 1 or 2 s.ds below the mean across all the tests (not including the Goldman-Fristoe). The other seven children in this group had scores in the normal range on either the vocabulary measure (one child) or on RNW (six children). Only three of the 13 children met the profile of performance (defined as more than 1 s.d. below the mean but less than 2) in the borderline subtype, indicating that this group is more heterogeneous, and less clearly defined as language impaired. The remaining children had scores in the normal range on vocabulary (four children) or RNW (five children) or both (one child).

The language test profiles for most of the children in the language-impaired subtype are particularly revealing about the nature of language impairments in autism. The pattern of their performance is strikingly similar to what has been reported for children with a SLI, a developmental language disorder that is diagnosed on the basis of per-

formance on language tests that fall significantly below age expectations, but in the absence of other conditions such as hearing loss, mental retardation, autism or frank neurological pathology. The patterns of performance shown in figure 1 match the profile found across these same kinds of tests in children with SLI (Tomblin & Zhang 1999). For example, scores on the vocabulary measures were somewhat higher than the CELF scores, indicating that lexical knowledge is generally less impaired than higher-order language abilities.

The most interesting finding was the poor performance by the children in the language-impaired subtype on RNW. Given that children with autism are known for their excellent echolalic skills, one might have predicted that, across the board, the children in this study would have done well on this test, as they did on the Goldman-Fristoe test. Figure 1 shows that this was clearly not the case: performance on RNW distinguished well between children with normal language ($M = 91$) and children with borderline ($M = 83$) or impaired ($M = 83$) language. This test was included in our language battery because it is one on which children with SLI demonstrate significant deficits (e.g. Gathercole & Baddeley 1990; Bishop *et al.* 1996; Dollaghan & Campbell 1998; Weismer *et al.* 2000). Indeed, poor performance on nonword repetition tests is now considered one of the primary clinical markers of SLI (Tager-Flusberg & Cooper 1999). Taken together, we argue that children with autism with language impairments, probably including many children in both the borderline and impaired subtypes identified in this study, have a language disorder that is overlapping with the disorder of SLI (see also Rapin 1998; Bishop & Norbury 2002).

(b) Study Ib: grammatical deficits in autism

Current research on SLI has identified another important clinical marker of this disorder. This second marker involves measures of children's knowledge and processing of finite-verb morphology. Several studies have found that children with SLI tend to omit several finite verb-related morphemes in obligatory contexts, including the third-person present tense *-s* (e.g. *Susan skip-s*) or the past-tense regular (e.g. *Susan walk-ed*) or irregular (e.g. *Susan left*) forms (Rice *et al.* 1995; Rice & Wexler 1996; Bedore & Leonard 1998). We followed up our findings of potential overlap between autism and SLI by exploring whether the children with autism in our initial study who fell into the language-impaired subtype would also show problems in marking tense (Roberts *et al.* 2000).

For this study, data were collected from 62 (54 boys and eight girls) of the children in the original sample of 89, 41 of whom had also participated in study Ia. They were given two experimental tasks, drawn from Rice and Wexler's groundbreaking work on tense in SLI (Rice *et al.* 1995). One task used linguistic probes to elicit the past tense, the other used probes to elicit the third-person singular present-tense marker. On the past-tense task, children were shown pictures of people engaged in activities and asked questions such as, 'What happened?' or 'What did he do with the rake?' There were 11 trials designed to elicit regular past-tense forms on lexical verbs (e.g. wash, colour) and eight intermixed trials to elicit irregular forms (e.g. catch, fall). On each trial the exper-

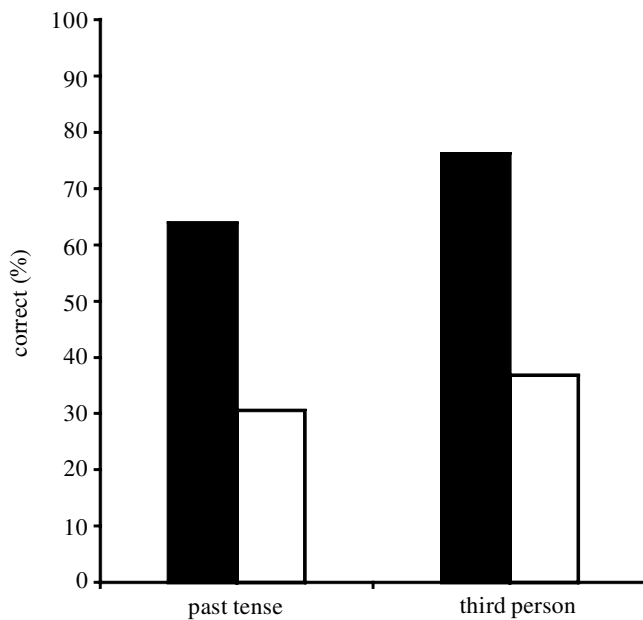


Figure 2. Performance on the past tense and third person present tense tasks by the normal and impaired language subtype groups. White bars, normal subtype; black bars, impaired subtype.

imenter first modelled the verb and then asked the probe questions. For the third-person task, 12 pictures depicting people in various occupations (e.g. doctor, painter) were presented to the children. They were asked questions such as: 'Tell me what a doctor does' and 'What does a painter do?'. Children were probed until they produced a verb in the third person (e.g. *He help(-s) people*).

The 62 children were divided into normal, borderline and impaired subtypes, based on standardized language test scores. Figure 2 shows the performance of the children on the tense-marking tasks for the normal (25 children; 40%) and impaired subtypes (20 children; 32%). The children in the normal language subtype gave almost twice as many correct responses as those in the impaired subtype, whose performance was between 30% and 40% correct on both tasks. Differences between the children in the impaired subtype and the other subtypes were highly significant on both the third-person singular ($F_{2,59} = 10.7$, $p < 0.0001$; impaired $<$ normal, $t(44) = 4.91$, $p < 0.0001$) and on the past tense ($F_{2,59} = 8.13$, $p < 0.001$; impaired $<$ normal, $t(44) = 3.93$, $p < 0.0001$). The most common error pattern was to omit any morphological marking on the verb stem, the error that is also most frequently reported for children with SLI. The children in the impaired subtype produced significantly more of these errors than the other children on the past-tense task ($F_{2,59} = 3.16$, $p < 0.05$; impaired $>$ normal, $t(44) = 2.25$, $p < 0.03$), but the differences between the groups did not reach significance on third-person singular ($F_{2,59} = 0.63$, n.s.). On the past-tense task the children were equally likely to produce these bare-stem errors on the regular and irregular verbs, and made few over-regularization errors (e.g. *fallen*). Again, studies on children with SLI report similar findings (Marchman *et al.* 1999; Rice 1999). The findings from this study provide further support for the view that autism and SLI are overlapping disorders in some, but not all, children with autism. Thus, this group

of children with SLI represents a subtype within autism because there are clearly children with autism but without any linguistic deficits, as in our normal language subtype (cf. Bishop 2000).

(c) Study 1c: morphometric analysis of brain asymmetry in autism

If there were a subtype in autism that is overlapping with SLI, defined on the basis of similar language phenotypes, then one would hypothesize that they would show similar atypical patterns of brain structure. Thus far there have been several studies of brain structure in SLI. The most consistent finding in studies of children and adults with SLI is that they show different patterns of brain asymmetry, as compared with non-SLI controls. In normal individuals, left (L) cortical regions, especially in key language areas (perisylvian region, planum temporale and Heschel's gyrus), are enlarged relative to the size of those regions in the right (R) hemisphere. By contrast, individuals with SLI or with language-based learning disorders show reduced or reversed asymmetries in these areas (Galaburda 1989; Jernigan *et al.* 1991; Plante *et al.* 1991; Leonard *et al.* 1996; Gauger *et al.* 1997; Clark & Plante 1998).

Our group has recently completed a MRI study comparing 16 boys with autism (all with normal NV IQ scores) to 15 age, sex and handedness matched normal controls who were part of a different cohort of children from those participating in the language studies described here (Herbert *et al.* 2002). MR scans were obtained on a 1.5 T scanner and included a T1-weighted sagittal scout series, a coronal T2-weighted sequence, and a coronal volumetric T1-weighted spoiled gradient echo-imaging sequence for morphometric analysis. The images were processed with custom software, and head position was normalized by re-slicing each volume with 3 mm thickness along the coronal plane, perpendicular to the anterior commissure–posterior commissure plane, without scaling the image size.

Neuroanatomic segmentation of grey and white matter and ventricles was performed using semi-automated procedures based on intensity contour mapping and differential intensity contour algorithms (for more details of the methods used see Filipek *et al.* 1994 and Caviness *et al.* 1996). The neocortical ribbon was then parcellated into 48 primarily gyral-based parcellation units per hemisphere (Kennedy *et al.* 1998). We compared the volumes in parcellation regions in the L and R hemispheres, expressed as a symmetry index. For each structure in the brain this index was calculated as: $[2 \times (L - R)/(L + R)] \times 100$.

We focused our group comparisons on the language regions of the cortex. In inferior lateral frontal language cortex (pars opercularis, associated with Broca's area) the boys with autism were significantly different from controls ($F_{1,30} = 5.58$, $p < 0.02$). This region was 27% larger in the R hemisphere in the boys with autism by contrast with the control boys, who had 17% larger volume in the L hemisphere. Other differences between the groups did not reach statistical significance. The reversed asymmetry found in the boys with autism is strikingly similar to what has been reported in studies of boys with SLI (e.g. Jernigan *et al.* 1991; Gauger *et al.* 1997). Unfortunately, language phenotypic data were not available for the boys

with autism in this study, and so individual difference patterns and relationships between brain and behavioural data could not be examined. Nevertheless, based on other reports from which this autistic sample was drawn, we know that it included primarily children with language impairments (Rapin 1996).

These three studies indicate that there is a subtype among children with autism who have a neurocognitive phenotype that is the same as has been reported in the literature for SLI. Children with autism in the language-impaired subtype performed poorly on standardized and experimental language tests that are sensitive to deficits that characterize SLI, and they showed the same reversal of asymmetry in frontal language regions of the brain. To what extent does the identification of this putative SLI subtype in autism have implications for genetic studies of autism? Studies have found among family members of children with autism, there are significantly elevated rates of documented histories of language delay and language-based learning deficits that go well beyond pragmatic difficulties (Bolton *et al.* 1994; Piven *et al.* 1997; Fombonne *et al.* 1997; Bailey *et al.* 1998). Twin studies have also reported that co-twins discordant for autism had high rates of language deficits that resemble the pattern described as SLI (Folstein & Rutter 1977; Le Couteur *et al.* 1996). There is also evidence that in families identified on the basis of having a child with SLI, there is a significantly elevated risk of autism among the siblings. Hafeeman & Tomblin (1999) recently reported that in a population-based sample of children diagnosed with SLI, 4% of the siblings met criteria for autism. This rate is much higher than would be expected based on the current prevalence estimates of *ca.* 1 in 500 (Fombonne 1999), and is similar to the 6% risk recurrence rates in autism families (Santangelo & Folstein 1999).

In addition to this behavioural evidence, recent genetic linkage and association studies may offer further clues to some shared genetic basis for these disorders. The KE family in England has been intensively investigated because they represent a large multi-generational pedigree in which a severe speech and language disorder has been transmitted in a manner indicating a single dominant gene. The locus of the gene was found on chromosome 7q31 (Fisher *et al.* 1998) and it has recently been identified as the FOXP2 gene (Lai *et al.* 2001). Tomblin and his colleagues took their population-based sample of children with SLI (Tomblin *et al.* 1998), and found a significant association between SLI and an allele of the CFTR gene. This gene is in the 7q31 region where FOXP2 is located, although more recent studies have not found an association between SLI and FOXP2 (Newbury *et al.* 2002; Meaburn *et al.* 2002). Nevertheless, there is some evidence from Tomblin *et al.* that there is a gene (or genes) located on the long arm of chromosome 7 that contributes to SLI. Another locus for a gene associated with SLI has been recently found on chromosome 13 (13q21), based on the analysis of five large pedigrees (Bartlett *et al.* 2002).

Genetics studies have consistently identified 7q31 as a region that is likely to include a susceptibility gene for autism (International Molecular Genetic Study of Autism Consortium 1998). However, it does not appear that FOXP2 is a candidate autism gene (Newbury *et al.* 2002;

Wassink *et al.* 2002). Another locus for a susceptibility gene for autism has been found on 13q (CLSA 1999). However, as noted earlier, all the genome scans conducted thus far have found only modest signals in all studies using linkage analysis. The parallels between the loci that have been linked to autism and SLI are striking, and recently the CLSA explored the possibility of incorporating a phenotypically defined subgroup in their genetic analysis (CLSA 2001). Using only the subgroup of probands with autism who had no language or clearly impaired language and whose parents had a history of language difficulties, the linkage signals on both 7q and 13q were significantly increased, indicating that these signals were mainly attributable to the language-impaired subtype within autism. These genetic findings hold out some promise that defining language phenotypic subtypes within the autism population may provide important benefits to genetic studies (cf. Dawson *et al.* 2002).

3. COGNITIVE PROFILES IN AUTISM

Autism is often characterized by unevenly developed cognitive skills. Unevenness in the cognitive abilities of individuals with autism has been most frequently documented in terms of IQ profiles. Although an IQ profile in which NV, visuospatial abilities are significantly superior to V abilities has been most strongly associated with autism (see Lincoln *et al.* 1988), this profile is not universal among individuals with autism, and is not even necessarily the modal cognitive profile in autism (Siegel *et al.* 1996). Further, higher-functioning individuals with autism often evidence V abilities that are superior to their visuospatial skills in IQ testing (Manjiova & Prior 1999; Ozonoff *et al.* 2000).

We conducted three additional studies that examined cognitive profiles in school-age children with autism, focusing particularly on discrepancies between V and NV skills. In the first study, we investigated whether any specific neurocognitive profile might be associated with increased susceptibility to autistic symptomatology and might thereby index important aspects of the underlying brain pathology. In the second and third study, we examined the relationship between cognitive profiles and two putative indices of autistic brain pathology: abnormally increased head circumference and brain volume.

(a) *Study IIa: cognitive profiles and symptom severity in autism*

Our first study (Joseph *et al.* 2002) investigated whether different cognitive profiles were associated with differences in the severity of the core communication and reciprocal social interaction symptoms in autism. The participants were 47 children (five girls and 42 boys) with DSM-IV clinical diagnoses of autism or PDDNOS, who ranged from 6 to 13 years in age (mean of 8 years 11 months). They were administered the ADI-R and ADOS by specially trained personnel who demonstrated reliability in scoring with the authors of the instruments and on-site trainers. All participants met criteria for autism on the ADI-R diagnostic algorithm. On the ADOS, 41 children met diagnostic criteria for autism, 5 children met criteria for a less severe diagnosis of ASD, and 1 child met criteria for ASD in the reciprocal social interaction domain, but

Table 1. Study IIa: age, IQ and ADOS scores as a function of V–NV discrepancy group.

	V–NV discrepancy group		
	V < NV (<i>n</i> = 16) <i>M</i> (s.d.)	V = NV (<i>n</i> = 18) <i>M</i> (s.d.)	V > NV (<i>n</i> = 13) <i>M</i> (s.d.)
age	8;6 (2;0)	8;9 (1;10)	9;7 (1;10)
full-scale IQ	91 (25)	77 (17)	87 (19)
V IQ	73 (22)	77 (17)	103 (19)
NV IQ	102 (24)	80 (15)	80 (16)
ADOS symptom severity			
communication	5.9 (1.6)	4.7 (2.1)	4.6 (1.6)
social interaction	11.0 (2.1)	8.6 (2.4)	8.2 (2.0)

not in the communication domain. Given that children met clinical diagnostic criteria for autism or PDDNOS, and ADI-R criteria for autism, we chose to include children who did not necessarily meet criteria for autism on the ADOS to allow for a wider range of variance in scores, which we were using as quantitative measures of current symptom severity. The communication and reciprocal social interaction scores from the ADOS diagnostic algorithms served as the dependent variables, with higher scores reflecting a greater degree of impairment.

To assess cognitive functioning, we used the DAS (Elliott 1990). The DAS consists of six core subtests that yield a V and a NV IQ score, which we have argued are conceptually more homogeneous and can provide a more valid estimate of differential cognitive abilities than the Wechsler (1991, 1997) Verbal and Performance subscales (Joseph *et al.* 2002). DAS V–NV difference scores were calculated by subtracting the NV IQ score from the V IQ score, and V–NV discrepancies were identified on the basis of the minimum difference between V and NV IQ scores required for significance at the 0.05 level of probability (Elliott 1990).

Analysis of children's cognitive profiles revealed a high rate of V–NV discrepancies (62%), which occurred at a much higher frequency than in the DAS normative sample (*ca.* 30%), and which occurred nearly equally in both directions. Of the 47 participants, 16 exhibited a V < NV profile, 13 exhibited a V > NV profile, and 18 exhibited no discrepancy. Table 1 displays mean age, IQ scores and ADOS scores for each of the V–NV discrepancy groups. The V–NV groups did not differ significantly in age, $F_{2,44} = 0.1$, *n.s.* A one-way ANOVA comparing the groups on full-scale IQ was not significant, $F_{2,44} = 2.0$, but pairwise comparisons showed a marginally significant difference ($p < 0.06$) between the V < NV group, which had the highest full-scale IQ, and the V = NV group, which had the lowest. As can be seen in table 1, the V and NV IQ scores for the two discrepancy groups were nearly the converse of each other, and the low score for each discrepancy group was similar to that found in the nondiscrepancy group. This pattern of scores indicated that the V–NV discrepancies reflected a genuine strength in one domain or the other, rather than differing levels of V ability across groups who shared the same level of NV ability.

Correlational analyses showed that V IQ was inversely related to ADOS communication score, $r(45) = -0.48$, $p < 0.01$, and social interaction score, $r(45) = -0.32$, $p < 0.05$.

Although NV IQ was unrelated to ADOS scores, the V–NV difference score was specifically correlated with the ADOS social interaction score, $r(45) = -0.45$, $p < 0.01$, such that the higher a child's NV IQ was relative to V IQ, the more impaired he or she was in reciprocal social functioning. This relationship remained significant even when absolute level of V ability was partialled from the correlation, $r(44) = -0.35$, $p < 0.05$.

A one-way MANCOVA was conducted to examine differences in ADOS symptom severity among the V–NV groups. As V IQ was correlated with ADOS scores, it was included as covariate in order to control for the effect of group differences in the absolute level of V ability. For communication symptoms, there was a significant effect of the covariate V IQ, $F_{1,45} = 8.74$, $p < 0.01$, but no effect of the V–NV group. By contrast, for social interaction symptoms, there was no effect of the covariate, but a significant effect of V–NV group, $F_{2,44} = 5.09$, $p < 0.02$. Pairwise comparisons showed that the ADOS social interaction score was significantly higher in the V < NV group than in the V = NV and V > NV groups, which did not differ from each other on this score.

In summary, we found a high rate of V–NV discrepancies in this group of children with autism, and these discrepancies were in favour of V ability nearly as often as NV ability. In addition, we found an interesting pattern of relationships between measures of cognitive ability and symptom severity. First, V ability was inversely related to symptoms in the reciprocal social interaction and, particularly, the communication domain. This finding is consistent with evidence that level of language functioning is an important mediating factor in the expression of autistic symptoms (Bailey *et al.* 1996). Our second and novel finding was that children with discrepantly superior NV skills exhibited increased impairments in reciprocal social skills that were independent of absolute level of V ability and overall ability. By contrast, children with cognitive discrepancies of a comparable magnitude, but in favour of V abilities, did not exhibit increased symptoms. One possibility could be that the children in the V > NV group were able to use their relatively superior V skills to help compensate for their deficits in the social interaction domain. However, although children in the nondiscrepancy group had V IQ scores that were much lower than in the V > NV group, and similar to those in the V < NV group, they were no more impaired in social-communicative functioning than children with relatively superior V skills. This has led us to argue (Joseph *et al.* 2002) that the imbalance in cognitive abilities represented by the V < NV profile

may reflect a particularly severe disturbance in brain development and organization and, as such, may provide a marker for an etiologically significant subtype of autism.

Although superior NV abilities in individuals with autism have traditionally been conceived in terms of a 'sparing' of visual-perceptual skills relative to V skills (Lincoln *et al.* 1988), a more recent, alternative view is that these apparently preserved skills are not achieved by virtue of a selective sparing of normal cognitive capacities and their neurobiological substrates, but are the outcome of fundamental differences in neurocognitive development and organization (Karmiloff-Smith 1997, 1998; Happé 1999). For example, enhanced visuoperceptual capacities in autism have been attributed to local processing biases resulting from a failure of the normal propensity for 'central coherence' (Frith & Happé 1994; Happé 1999) or, alternatively, from the abnormal development of lower-level perceptual processes (Plaisted *et al.* 1998; Plaisted 2000; Elgar & Campbell 2001). Efforts to link these functional abnormalities or differences to their neuroanatomical underpinnings has recently given rise to the hypothesis that isolated visuoperceptual skills in autism may be related to increased neuronal growth or reduced cortical pruning and connectivity (Cohen 1994; Happé 1999). One way of testing this hypothesis, at least indirectly, would be to examine whether discrepantly strong NV skills in autism are associated with increased head and brain size.

(b) *Study IIb: cognitive correlates of large head circumference in autism*

Enlarged head circumference, or macrocephaly, occurs at an unusually high frequency among children with autism and their nonautistic relatives (Davidovitch *et al.* 1996; Woodhouse *et al.* 1996; Lainhart *et al.* 1997; Stevenson *et al.* 1997; Fombonne *et al.* 1999; Fidler *et al.* 2000). However, efforts to link macrocephaly to other clinical and cognitive features of autism have proven largely unsuccessful, raising doubts as to whether macrocephaly indexes a homogeneous and etiologically meaningful autism subtype. In this study (Deutsch & Joseph 2003), we examined the relationship between head circumference in autism and a wide range of potential clinical and cognitive correlates, including V–NV difference scores.

Participants were 63 children (54 males) with DSM-IV clinical diagnoses of autism or PDDNOS, who ranged from 4 to 14 years in age (mean of 7 years 4 months). All children met criteria for autism on the ADI-R, and for either autism ($n = 58$) or ASD ($n = 5$) on the ADOS. Of the 63 participants, 25 had also participated in study IIa, described in § 3a. Head measurements included circumference, length and width, all of which were converted to standardized (z) scores, adjusted for age and sex using the Farkas (1994) database. Other measures included DAS V IQ, NV IQ and V–NV difference score; expressive and receptive language; executive functions; and ADOS symptom severity.

Using the conventional clinical criterion of $z > 1.88$ (i.e. > 97 th percentile), we found that macrocephaly occurred at a rate of 14% in our sample, which was significantly higher than the expected rate of 3%, $\chi^2(1, N = 63) = 27.57, p < 0.001$ and similar to rates reported in several previous studies (Lainhart *et al.* 1997; Fom-

bonne *et al.* 1999). Large head size ($z > 1.28, > 90$ th percentile) that did not necessarily meet the criterion for macrocephaly was also common, occurring at a rate of 33%, which was much higher than the expected rate of 10%, $\chi^2(1, N = 63) = 38.11, p < 0.001$. By contrast, microcephaly did not occur at a rate higher than expected.

Correlational analyses revealed a significant inverse relationship between head circumference and V–NV difference scores, $r(57) = -0.38, p < 0.01$, indicating that children with larger head circumference tended to have discrepantly higher NV scores on the DAS. This relationship remained significant when absolute level of V ability (V IQ score) was partialled from the correlation, $r(56) = -0.35, p < 0.02$. (Only 59 of the original 63 participants were included in these analyses because four children were not of sufficient cognitive ability to generate separate V and NV IQ scores.) Head circumference was not correlated with age, V or NV IQ, language, executive functions or ADOS symptom severity.

Table 2 displays mean age, IQ and standardized head circumference scores for each V–NV profile group, defined using the same criteria as in study IIa. The groups did not differ significantly in age, $F_{2,56} = 2.32, n.s.$ An ANCOVA covarying V IQ revealed no effect of the covariate, $F_{1,56} = 1.19, n.s.$, but did show a main effect of V–NV group on head circumference, $F_{2,56} = 3.69, p < 0.05$. Pairwise comparisons showed that head circumference was significantly larger in the $V < NV$ group than in the $V = NV$ and $V > NV$ groups, which did not differ from each other in head circumference.

We conducted *post-hoc* analyses to examine whether the V–NV profile groups differed in head width, length or both. A one-way MANOVA showed a significant effect of V–NV group on head width, $F_{2,56} = 3.52, p < 0.05$, but not on head length, $F_{2,56} = 1.75, n.s.$ Table 2 displays mean standardized head width and length for each V–NV group.

In summary, we identified a subgroup of children with autism who have discrepantly high NV skills accompanied by large head circumference, thus providing further evidence that the $V < NV$ profile may index an etiologically significant subtype of autism. This finding indicates that macrocephaly and unevenly developed NV skills reflect the same underlying disturbance in neurocognitive development and organization. Although preliminary and in need of replication, these results are consistent with suggestions that isolated visual-perceptual skills in autism may be related to neuronal overgrowth or reduced neuronal pruning and connectivity (Cohen 1994; Happé 1999). Recent evidence supporting this possibility includes the finding that there is disproportionate growth of the posterior cerebral cortex in autism (Piven *et al.* 1996), and the finding that enlarged head circumference in autism is primarily due to an increase in head width (Deutsch *et al.* 2003). Increased head width in autism would be consistent with enlargement of parieto-temporal cortex and is conceivably related to abnormal development of the visuoperceptual skills mediated by these brain regions. In keeping with this possibility, the $V < NV$ group in this study was differentiated from the other groups by head width rather than length. However, more detailed, regional measurements of brain volume in macrocephalic

Table 2. Study IIB: age, IQ scores and head size as a function of V–NV discrepancy group.

	V–NV discrepancy group		
	V < NV (<i>n</i> = 27) <i>M</i> (s.d.)	V = NV (<i>n</i> = 21) <i>M</i> (s.d.)	V > NV (<i>n</i> = 11) <i>M</i> (s.d.)
age	6;8 (2;0)	7;8 (2;4)	8;3 (2;10)
full-scale IQ	84 (19.3)	73 (17.2)	73 (18.3)
V IQ	72 (16.8)	74 (17.3)	89 (18.8)
NV IQ	97 (18.5)	75 (16.0)	66 (17.8)
head circumference ^a	1.3 (1.2)	0.3 (1.4)	0.1 (1.3)
head width	1.0 (1.1)	0.6 (0.8)	0.01 (1.0)
head length	0.3 (1.1)	–0.1 (0.9)	–0.2 (0.9)

^a All head measurement figures are based on standardized *z*-scores.

Table 3. Study IIC: age, IQ and brain volumes (cm³) as a function of V–NV discrepancy group.

	V < NV (<i>n</i> = 8) <i>M</i> (s.d.)	V = NV (<i>n</i> = 8) <i>M</i> (s.d.)	<i>t</i> (14)	<i>p</i>
age	9;10 (2;3)	10;0 (1;8)	0.2	n.s.
full-scale IQ	89 (25)	87 (15)	0.2	n.s.
V IQ	75 (18)	89 (17)	1.6	n.s.
NV IQ	101 (25)	88 (14)	1.3	n.s.
total brain	1530 (87)	1385 (139)	2.5	< 0.05
cerebrum	1347 (78)	1212 (132)	2.5	< 0.05
cerebral cortex	814 (61)	719 (66)	3.0	< 0.01
cerebral white matter	454 (28)	419 (70)	1.3	n.s.
cerebellum	156 (11)	149 (11)	1.2	n.s.
cortical regions				
frontal cortex	272 (18)	244 (27)	2.4	< 0.05
parietal cortex	133 (14)	119 (10)	2.3	< 0.05
temporal cortex	174 (15)	147 (17)	3.4	< 0.01
occipital cortex	160 (18)	142 (12)	2.3	< 0.05
paralimbic cortex	68 (5)	61 (6)	2.4	< 0.05

children with autism would be necessary to determine if these phenomena are truly related.

(c) Study IIC: V–NV discrepancies and brain volume in autism

Given prior evidence that increased head size is associated with increased brain volume in autism (Deutsch *et al.* 2001), the purpose of this final study was to determine:

- (i) if the V < NV profile is associated with increased brain volume in autism; and
- (ii) if there is any pattern of regional brain enlargement specifically associated with the V < NV profile in autism.

Participants were 16 male children with DSM-IV clinical diagnoses of autism or PDDNOS. All children met the criteria for autism on the ADI-R, and had been participants in study IIB. The sample was evenly divided between children who manifested a V < NV discrepancy on the DAS and those who did not. As can be seen in table 3, the two groups were well-matched on age and full-scale IQ ($p > 0.8$). Brain scans were acquired and analysed in a similar way to those described in study Ic.

We conducted a series of exploratory *t*-tests to assess potential differences in brain volumes between the two

groups. As can be seen in table 3, total brain volume was significantly higher in the V < NV group than in the V = NV group, $t(14) = 2.5$, $p < 0.05$. In order to assess whether the increase in total brain volume was generalized across brain structures, we compared group differences in cerebral volume to those in cerebellar volume. Cerebral volume was significantly higher in the V < NV group, $t(14) = 2.5$, $p < 0.05$, but there was no difference between the groups in cerebellar volume, $t(14) = 1.2$, n.s. Subsequent analyses showed that the group differences in cerebral volume were due to differences in cortical grey matter, $t(14) = 3.0$, $p < 0.01$, rather than in cerebral white matter, $t(14) = 1.3$, n.s. In a final set of analyses, we examined whether increased cortical volume in the V < NV group was specific to any region(s) of the cortex. As shown in table 3, the increases in cortical volume found in the V < NV group were generally consistent across the frontal, parietal, temporal and occipital lobes, and the paralimbic cortex.

In summary, this final study provides evidence linking the V < NV profile to enlarged brain volume in addition to enlarged head circumference. Although our preliminary evidence indicates that the increases in brain volume associated with discrepantly strong visual–spatial skills primarily affect cortical grey matter, we were not able to identify any pattern of regional differences in cortical size.

4. SUMMARY AND CONCLUSIONS

We have presented evidence for two different subtypes in autism—one based on language abilities and the other based on IQ discrepancy scores. Our behavioural studies indicate that there is a subtype in autism that overlaps with SLI. In a separate study of brain structure, we found reversed asymmetry in a group of boys with autism in the frontal language area, a pattern similar to that found in SLI. Our data thus far do not permit a direct link between the SLI subtype and the reversed asymmetry, but this is clearly an important direction for future studies on this language subtype within autism. Discrepantly high NV IQ scores were shown to be related to autism severity, and to larger head size and brain volume. Genetic studies of autism have found that dividing samples on the basis of language impairment (although the phenotypes used in the CLSA (2001) study were more crudely defined than those presented here) may be useful for identifying genes associated with this component of autistic disorder. As yet, no genetic studies have attempted to use IQ discrepancy scores, so we do not know whether the subtype with high NV IQ represents one that is meaningful for genetic studies of autism.

As research advances on the etiology of autism, more detailed information about the phenotypes of probands promises to speed the search for specific autism genes. Thus far, we have focused on cognitive and behavioural data for defining phenotypes in autism. Adding structural and functional brain data will help to bridge the connection between genes and behaviour and will advance our understanding of how mutations in genes associated with autism lead to abnormalities in brain development that are expressed in different patterns of behaviour.

There are many questions that remain regarding the putative subtypes presented here. For example, are they qualitatively distinct subtypes, as we have argued, or do they represent quantitative variation along dimensions that we have measured using psychometric tests? Do these phenotypic subtypes extend to family members, and can they thus be considered ‘endophenotypes’ for autism (cf. Leboyer *et al.* 1998)? As more studies are conducted on these and other components of the autism phenotype, genuine progress will be made in uncovering its underlying causes, which in turn will lead to important advances in developing novel and effective treatments for this devastating disorder.

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GLOSSARY

ADI-R: autism diagnostic interview—revised

ADOS: autism diagnostic observation schedule

ASD: autism spectrum disorder

CELF: clinical evaluation of language fundamentals—pre-school or III

CLSA: collaborative linkage study of autism

DAS: differential abilities scale

EVT: expressive vocabulary test

IQ: intelligence quotient

MRI: magnetic resonance imaging

NV: non-verbal

PDDNOS: pervasive developmental disorder not otherwise specified

PPVT: Peabody picture vocabulary test—III

RNW: repetition of nonsense words

SLI: specific language impairment

V: verbal