Identifying neurocognitive phenotypes in autism

Helen Tager-Flusberg* and Robert M. Joseph

Laboratory of Developmental Cognitive Neuroscience, Department of Anatomy and Neurobiology,
Boston University School of Medicine, 715 Albany Street L-814, Boston, MA 02118, USA

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: 

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 is 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) that 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 two to ten 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 using advances in human genome research and molecular biology (see Lamb et al. 2000; Rutter 2000; Folstein & Rosen-Shiffley 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. 1999; 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...
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; Tager-Flusberg et al. 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. Barrak et al. 1978). 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 factors are more variable, 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 I: 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 23 (foot) to 114.

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 Gold- man-Fristoe Test of Articulation (Goldman & Fristoe 1986) that measures the accuracy of productive phonology for the consonant sounds of English, and the RNW taken from the NEPSY (Korkman et al. 1999). 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 (Wig 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, 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. 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 2 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
Neurocognitive phenotypes in autism. H. Tager-Flusberg and R. M. Joseph

Figure 1. The profile of performance on language tests by language subtypes. Diamonds, CELF total; squares, PPVT + RVT; triangles, Goldman-Fristoe test; circles, RNW.

were highly correlated with one another and the tests were normed on the same sample. At a group level, the children 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 ($F_{2,44} = 19.45$, $p < 0.001$), but did not reach significance on the RNW ($F_{2,44} = 1.77$, n.s.). The impaired children did not have deficits in basic articulation skills, as can be seen by their scores on the Goldman-Fristoe, which fell within the normal range; this was confirmed in a one-way ANOVA showing no differences among the subtypes on this test ($F_{2,44} = 0.82$, 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 fit 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.d.s 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 development-
irregular forms (e.g. catch, fail). On each trial the experimenter 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 helps (-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 ($F_{1,25} = 10.7$, $p < 0.0001$; impaired < normal, $t(44) = 4.91$, $p < 0.0001$) and on the past tense ($F_{1,25} = 8.13$, $p < 0.001$; 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 found 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 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 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; Gaugier 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 (Marchman et al. 2003). 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 reslicing each volume with 3 mm thickness along the coronal plane, perpendicular to the AC-PC 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 ($F_{1,38} = 5.58$, $p < 0.02$). This region was 27% larger in the R hemisphere in the boys with autism by contrast to 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; Gaugier 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 dif-

There is also evidence that in families identified
on the basis of having a child with SLI, there is a signifi-
cantly elevated risk of autism among the siblings. Hate-
man & 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
Kallmann family in England has been intensively investi-
gated 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 domi-
nant gene. The locus of the gene was found on chromo-
some 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 sig-
nificant association between SLI and an allele of the
CPT2 gene. This gene is in the 7q31 region where
FOX2 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 13
that contributes to SLI. Another locus for a gene associated
with SLI has been recently been found on chromosome
13 (13q21), based on the analysis of five large pedigrees
(Bartlett et al. 2002).

Genetic studies have consistently identified 13q14 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
FOX2 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
due to this severe diagnosis of 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 PROFILING IN AUTISM

Autism is often characterized by unevenly developed
cognitive skills. Unevenness in the cognitive abilities of
individuals with autism has been most frequently docu-
mented 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 univer-
sal among individuals with autism, and is not even neces-
sarily 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 (Manjova & Prior 1999;
Ozono 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 spe-
cific 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 exam-
ined the relationship between cognitive profiles and two
putative indices of autistic brain pathology, abnormally
increased head circumference and brain volume.

(a) Study I: 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 (13 girls and 24 boys) with DSM-IV clinical
diagnoses of autism or PDDNOS, who ranged from 6 to 15.11 in age (M = 8.11). They were adminis-
tered 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, five children met criteria for a less severe diagnosis
of ASD, and one child met criteria for ASD in the recipro-
cal social interaction domain, but not in the communi-
cation domain. Given that children met clinical diagnostic
criteria for autism or PDDNOS, and ADI-R criteria for

Pol. Trans. R. Soc. Lond. B
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, \( F_{1,44} = 8.74, p < 0.01 \), 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, \( F_{1,44} = 5.09, p = 0.02 \). Pairwise comparisons showed that the ADOS social interaction score was significantly higher in the V−NV group than in the NV group 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 discrepancy 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 sub-
type 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. 1998), 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 neuropsychological 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 'cen-
tral 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 func-
tional abnormalities or differences to their neuroanatom-
ical 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; Stev-
enson et al. 1997; Fombonne et al. 1999; Fidler et al.
2000). However, efforts to link macrocephaly to other
clinical and cognitive features of autism (see the studies
cited earlier) have proven largely unsuccessful, rais-
ing doubts as to whether macrocephaly indexes a hom-
ogenous 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 4.4 to 14.0 (M = 7.4) in age. 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; execu-
tive functions; and ADOS symptom severity.

Using the conventional clinical criterion of z > 1.88
(i.e. > 97th percentile), we found that macrocephaly
occurred at a rate of 14% in our sample, which was sig-
nificantly higher than the expected rate of 5%, $\chi^2(1, N = 63) = 27.57, p < 0.001$ and similar to rates reported
in several previous studies (Lainhart et al. 1997; Fom-
bonne et al. 1999). Large head size (z > 1.28, > 90th
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,
macrocephaly did not occur at a rate higher than expected.

Correlational analyses revealed a significant inverse
relationship between head circumference and V–NV dif-
ference 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 relation-
ship remained significant at 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 corre-
lated 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, $F_{1,58} = 2.32, n.s.$ An
ANCOVA covarying V IQ revealed no effect of the covar-
iate, $F_{1,54} = 1.19, n.s.$, but did show a main effect of V–
NV group on head circumference, $F_{1,58} = 3.69, p < 0.05$.
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, $F_{1,54} = 3.52, p < 0.05$, but
not on head length, $F_{1,54} = 1.75, n.s.$ 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 evi-
dence 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 devel-
opment 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 neu-
ronal 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 (Pyren 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 develop-
ment 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
children with autism would be necessary to determine if
these phenomena are truly related.
Table 2. Study IIb: age, IQ scores and head size as a function of V–NV discrepancy group.

<table>
<thead>
<tr>
<th>V–NV discrepancy group</th>
<th>V &lt; NV (n = 27) M (s.d.)</th>
<th>V = NV (n = 21) M (s.d.)</th>
<th>V &gt; NV (n = 11) M (s.d.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>age</td>
<td>6.8 (2.0)</td>
<td>7.8 (2.4)</td>
<td>8.3 (2.10)</td>
</tr>
<tr>
<td>full scale IQ</td>
<td>84 (19.3)</td>
<td>73 (17.2)</td>
<td>73 (18.3)</td>
</tr>
<tr>
<td>V IQ</td>
<td>72 (16.8)</td>
<td>74 (17.3)</td>
<td>89 (18.8)</td>
</tr>
<tr>
<td>NV IQ</td>
<td>91 (18.5)</td>
<td>75 (16.6)</td>
<td>66 (17.8)</td>
</tr>
<tr>
<td>head circumference*</td>
<td>1.3 (1.2)</td>
<td>0.3 (1.4)</td>
<td>0.1 (1.3)</td>
</tr>
<tr>
<td>head width</td>
<td>1.0 (1.1)</td>
<td>0.6 (0.8)</td>
<td>0.01 (1.0)</td>
</tr>
<tr>
<td>head length</td>
<td>0.3 (1.1)</td>
<td>-0.1 (0.9)</td>
<td>-0.2 (0.9)</td>
</tr>
</tbody>
</table>

* 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.

<table>
<thead>
<tr>
<th>V–NV discrepancy group</th>
<th>V &lt; NV (n = 8) M (s.d.)</th>
<th>V = NV (n = 8) M (s.d.)</th>
<th>t(14)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>age</td>
<td>9.10 (2.5)</td>
<td>10.0 (1.8)</td>
<td>0.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>full scale IQ</td>
<td>89 (25)</td>
<td>87 (15)</td>
<td>0.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>V IQ</td>
<td>75 (18)</td>
<td>89 (17)</td>
<td>1.6</td>
<td>n.s.</td>
</tr>
<tr>
<td>NV IQ</td>
<td>101 (25)</td>
<td>88 (14)</td>
<td>1.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>total brain</td>
<td>1530 (87)</td>
<td>1385 (139)</td>
<td>2.5</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>cerebrum</td>
<td>1347 (78)</td>
<td>1212 (132)</td>
<td>2.5</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>cerebral cortex</td>
<td>814 (61)</td>
<td>719 (66)</td>
<td>3.0</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>cerebral white matter</td>
<td>494 (28)</td>
<td>419 (70)</td>
<td>1.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>cerebellum</td>
<td>156 (11)</td>
<td>149 (11)</td>
<td>1.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>cortical regions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>frontal cortex</td>
<td>272 (18)</td>
<td>244 (27)</td>
<td>2.4</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>parietal cortex</td>
<td>133 (14)</td>
<td>119 (10)</td>
<td>2.3</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>temporal cortex</td>
<td>174 (15)</td>
<td>147 (17)</td>
<td>3.4</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>occipital cortex</td>
<td>160 (18)</td>
<td>142 (12)</td>
<td>2.3</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>paralimbic cortex</td>
<td>68 (5)</td>
<td>61 (6)</td>
<td>2.4</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

(e) 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 was 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 discrepancy strongly 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. Discrepancy 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.

This research was supported by grants from the National Institutes of Health (NIDCD: PO1 DC 03610; NINDS: RO1 NS 38668), and was conducted as part of the NICHD-NIDCD funded Collaborative Programs of Excellence in Autism. The authors thank the following individuals for their assistance in preparing the data reported in this paper, and the manuscript: S. Hodge, L. McGrath, L. Stetser and A. Verbalis. They are especially grateful to the children and families who participated in this research.

REFERENCES


Lord, C., Riss, L., Lambrecht, L., Cook, E. H., Lenventhal, B. L., DiLavore, P. S., Pickles, A. & Rutter, M. 2000 The...
Neurocognitive phenotypes in autism

H. Tager-Flusberg and R. M. Joseph


**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
- KLE: magnetic resonance imaging
- NEPSY: magnetic resonance imaging
- MRI: magnetic resonance imaging
- NV: nonverbal
- PPVT: Peabody picture vocabulary test—III
- RNW: repetition of nonsense words
- SLI: specific language impairment
- V: verbal
- L: left