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Brief Report: Cognitive Correlates of Enlarged Head Circumference in Children with Autism

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This study examined the frequency and cognitive correlates of enlarged head circumference in a sample of 63 children with autism between the ages of 4 and 14. Consistent with prior evidence, macrocephaly occurred at a significantly higher frequency than in a normal reference sample. Head circumference was not associated with language or executive functioning, nor was it related to verbal or nonverbal IQ. Head circumference was, however, correlated with discrepancies between verbal and nonverbal IQ scores, independent of absolute level of verbal ability. Children with discrepantly high nonverbal abilities had a mean standardized head circumference that was more than 1 *SD* greater than in the reference sample, and that was significantly greater than in autistic children with a relative verbal advantage or no discrepancy in cognitive abilities, for whom mean head circumference was within normal limits. This convergence of physical and cognitive features suggests a possible etiologically significant subtype of autism.

KEY WORDS: Autism; head circumference; IQ; macrocephaly.

INTRODUCTION

Autism is thought to be heterogeneous in its etiology as well as its symptomatology (Folstein & Piven, 1991, Rutter, 2000). One proposed approach to resolving heterogeneity has been subgrouping on the basis of associated traits, ones that may reflect the broader autistic phenotype (Bailey, Phillips, & Rutter, 1996). One of these "endophenotypes" under wide investigation is macrocephaly, operationally defined as large head circumference, which has been found to be over-represented in autism (Bailey *et al.,* 1995; Bolton *et al.*, 1994; Davidovitch, Patterson, & Gartside, 1996; Deutsch *et al.,* in press; Fombonne, Rogé, Claverie, Courty, & Frémolle, 1999; Lainhart *et al.,* 1997; Stevenson, Schroer, Skinner, Fender, & Simensen, 1997; Woodhouse *et al.,* 1996). Recently, we reported that macrocephaly in children with autism is primarily characterized as an increase in head width but not length (Deutsch *et al.*, in press), and that this disproportionate increase in cranial dimension corresponds to brain size, imaged by magnetic resonance (Deutsch *et al.,* 2001). Macrocephaly is prevalent not only among probands, but also among the nonautistic relatives of autistic probands (Deutsch *et al.,* in press; Fidler, Bailey, & Smalley, 2000; Stevenson *et al.,* 1997), again suggesting its relevance to the study of the broader autism phenotype.

In the present study, we sought to determine whether large head size is reliably associated with other clinical or cognitive characteristics of children with autism. Such evidence would provide support for the hypothesis that macrocephaly indexes an autism subtype, and could shed light on the neurocognitive and etiological significance, if any, of enlarged head size in autism. To date, efforts to link macrocephaly to other features of autism have produced mostly null results.

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For example, macrocephaly in autism has not been found to be associated with language functioning (Davidovitch *et al.,* 1996; Lainhart *et al.,* 1997), full-scale or nonverbal IQ (Davidovitch *et al.,* 1996; Fombonne *et al.,* 1999; Lainhart *et al.*, 1997; Stevenson *et al.,* 1997; Woodhouse *et al.*, 1996), or severity of autistic symptoms (Fombonne *et al.,* 1999; Woodhouse *et al.,* 1996), with the exception of the finding of Lainhart *et al*. (1997) of a small, inverse relationship between head size and symptom severity as measured on the Autism Diagnostic Interview (Le Couteur *et al.,* 1989).

In this study we examined several potential correlates of head size in a sample of verbal and relatively high-functioning children with autism. Variables considered included verbal and nonverbal cognitive ability, language level, executive functions, and symptom severity.

METHODS

Participants

The study included 63 children (54 males, 9 females) with autism, from 4.4 to 14.0 years of age, whose families were recruited from community sources and ascertained on a single affected child. Only Caucasian children were included because reference norms for head circumference were not available for non-Caucasian children. The reported data were collected as part of a large, multidisciplinary research program on language functioning in autism at the Eunice Kennedy Shriver Center and Boston University Medical Center. The majority of participants were included as a subsample in the Deutsch *et al*. (in press) multisite study cited above.

All participants met criteria for autism on the Autism Diagnostic Interview–Revised (ADI-R) (Lord, Rutter, & LeCouteur, 1994) and were clinically confirmed to meet DSM-IV criteria (American Psychiatric Association, 1994) for autism or pervasive developmental disorder–not otherwise specified (PDD-NOS). In addition, all participants met the criteria for autism ($n = 58$) or for a less severe diagnosis of autism spectrum disorder ($n = 5$) on the Autism Diagnostic Observation Schedule (ADOS) (Lord, Rutter, DiLavore, & Risi, 1999). Children with Rett's syndrome, childhood disintegrative disorder, or autism-related medical conditions (e.g., neurofibramatosis, tuberous sclerosis, fragile-X syndrome) were not included in this study. Although the level of spontaneous language functioning varied significantly among participants, all children had at least acquired phrase speech, specified on the ADI-R as the spontaneous, flexible use of at least two words in combination, one of which must be a verb. Participant characteristics are detailed in Table I.

Measures

Head Circumference

Head circumference was measured using a plastic tape measure, pulled tightly across the occiput, corresponding to the occipital pole, and glabella, medially placed between the supraorbital rims (Deutsch & Farkas, 1994). Spreading calipers (GPM, Zurich, Switzerland) were used to measure cranial length (the linear distance between the glabella and occiput) and width (the linear distance between the eurions, right and left, corresponding to the biparietal diameter). Laboratory personnel established high inter-rater reliability for these measures, with intraclass correlations for circumference, length, and width of .99, .97, and .99, respectively. All head measurements were converted to standardized (z-) scores, adjusted for age and sex using the normative database created by Farkas (1994).

Table I. Participant Characteristics ($n = 63$)

	M	*SD*	Range
Age ($n = 63$)	7;4	2;3	4;4–14;0
ADI-R ($n = 63$)			
Communication	17.5	3.7	8–25
Social	22.1	4.3	10–29
Repetitive Behaviors	6.6	2.5	3–12
Head Circumference[a] ($n = 63$)	.71	1.3	−2.8–4.0
IQ			
Full-scale ($n = 63$)	76	20.4	25–118
Verbal ($n = 59$)	76	18.3	51–118
Nonverbal ($n = 59$)	84	21.3	43–153
V-NV difference score[b] ($n = 59$)	−8.0	20.0	−51–35
Language			
PPVT-III ($n = 63$)	76	20.7	40–134
EVT ($n = 63$)	73	19.9	40–114
Mean length of utterance ($n = 54$)	3.3	.83	1.6–5.2
Executive functions			
Working memory/inhibitory control ($n = 36$)	22.4	6.9	2–31
Planning ($n = 39$)	6.6	3.9	2–15
ADOS symptom severity ($n = 63$)	15.9	3.6	8–22

[a] Calculated as a z-score based on normative data from Farkas (1994).
[b] Calculated by subtracting the DAS nonverbal standard score from the DAS verbal standard score.

Differential Ability Scales (DAS)

The DAS (Elliott, 1990) is a cognitive assessment test that consists of a Preschool battery for children aged 2.6 to 6.11 and a School-Age battery for children aged 6.0 to 17.11. Each battery consists of six core subtests that yield full-scale, verbal, and nonverbal IQ scores. The DAS has several features that make it a particularly useful cognitive assessment for children with autism and other developmental disabilities. These include a downward extension of possible standard scores to 25 and a relatively brief administration time. In addition, the DAS subscales were designed to tap conceptually homogenous skills, and are arguably less confounded by the typical patterns of subtest scatter (e.g., high score on Block Design and low score on Picture Arrangement) that have been found for autistic individuals tested on the Wechsler Performance scale (Happé, 1994; Lincoln, Courshesne, Kilman, Elmasian, & Allen, 1988).

DAS verbal-nonverbal (V-NV) difference scores were calculated by subtracting the nonverbal IQ score from the verbal IQ score. V-NV discrepancies were identified on the basis of the minimum difference of 14 points required for significance at the .05 level of probability (Elliott, 1990). For the remaining variables, to reduce error associated with multiple comparisons, several composite measures were formed, each of which was justified by the intercorrelation of its component measures.

Language

Language measures included the Peabody Picture Vocabulary Test (PPVT-III) (Dunn & Dunn, 1997), the Expressive Vocabulary Test (EVT) (Williams, 1997), and mean length of utterance (MLU) (Brown, 1973) derived from a natural language sample. The PPVT-III measures receptive vocabulary. The child is presented with a spoken word and is asked to pick the corresponding picture. The EVT measures expressive vocabulary by asking the child to name pictures and, as the test advances, to provide synonyms for the pictured objects. Because scores on the PPVT-III and EVT are highly correlated, and the tests were developed with the same normative sample, we averaged the standard scores from these tests to generate a single vocabulary score.

Mean Length of Utterance (MLU) was calculated as the mean number of morphemes per utterance, based on the first 100 consecutive, nonimitative utterances spoken by the child in a naturalistic play situation with a parent. MLU is a standard measure of productive language capacity and morphological/syntactic development (Brown, 1973) and has been used to assess language development in children with autism (Tager-Flusberg *et al.,* 1990).

Executive Functions

Executive functions encompass a variety of mental operations required for complex, goal-directed behavior, including working memory, inhibitory control, and planning. Three measures of executive function were administered: Day-Night Stroop test, NEPSY Knock and Tap, and NEPSY Tower of London. In the Day-Night Stroop test (Gerstadt, Hong, & Diamond, 1994), the child is instructed to say "day" to a picture of the moon and stars and "night" to a picture of the sun. In NEPSY Knock and Tap (Korkman, Kirk, & Kemp, 1998), children are instructed to knock with their knuckles on the table when the examiner taps with flat palm, and vice versa. Both of these tasks require the child to keep a rule in mind, and inhibit a prepotent response (to name the picture, to copy the hand movement of the examiner). Raw scores from the Day-Night Stroop and Knock and Tap tests were combined to form a composite measure of working memory/inhibitory control (see Diamond, Prevor, Callender, & Druin, 1997).

NEPSY Tower (Korkman *et al.*, 1998) is modeled after Shallice's (1992) Tower of London. The child is asked to rearrange three different colored balls situated on three vertical pegs to reach a goal state, shown in a picture, in a prescribed number of moves without violating the rules (moving only one ball at a time, and only from one peg to another). This task is considered a measure of problem-solving and planning, but also requires working memory (maintaining rules and the necessary sequence of moves in mind) and inhibitory control (not placing balls directly on target pegs). Total raw score was used as a measure of planning.

Symptom Severity

Severity of impairment in social-communicative functioning was assessed using the Autism Diagnostic Observation Schedule (ADOS) (Lord *et al.*, 1999). The ADOS is a semistructured, experimenter-administered, interactive observation schedule that provides quantitative ratings of communicative and social behaviors corresponding to DSM-IV (APA, 1994) and ICD-10 (WHO, 1993) criteria for autism. The schedule consists of four developmentally sequenced modules, only one of which is administered, depending on the examinee's age and/or expressive language

level. Total score on communication and social diagnostic algorithm items served as the dependent variable in this study. Higher scores reflected a greater degree of impairment.

Number of participants, mean score and *SD* is reported for each variable in Table I. Four children were of insufficient ability to generate reliable subscale and corresponding V-NV difference scores on the DAS. In addition, many children were unable to master the brief instructional and/or training components of the executive functions tasks, and their data were therefore not included in statistical analyses.

RESULTS

Frequency of Macrocephaly

Using the conventional clinical criterion of $z > 1.88$ (i.e., >97th percentile), we found that macrocephaly occurred at a rate of 14%, which was significantly higher than the expected rate of 3% [$\chi^2(1, n = 63) = 27.57$, $p < .001$] and similar to rates reported in several prior studies (Deutsch *et al.*, in press: Fombonne *et al.*, 1999; Lainhart *et al.*, 1987). As shown in Table II, 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%, [$\chi^2(1, n = 63) = 38.11$, $p < .001$]. In contrast, microcephaly did not occur at a rate higher than expected.

Correlates of Head Circumference

Pearson product-moment correlations between head circumference and cognitive and clinical variables are displayed in Table III. As illustrated in Fig. 1, there was a significant inverse relationship between head circumference and V-NV difference scores [$r(57) = -.38$, $p < .01$], indicating that children with larger head circumference tended to have discrepantly higher nonverbal scores on the DAS. This relationship remained significant when absolute level of verbal ability (verbal IQ score) was partialled from the correlation [$r(56) = -.35$, $p < .02$]. Head circumference was not correlated with age, full-scale, verbal, or nonverbal IQ or with language, executive functions, or social-communicative functioning scores.

Table II. Distribution of Head Circumference in 63 Children with Autism

Head circumference percentile	No. of participants	Percent of sample
<3 (microcephalic)[a]	2	3
<10	4	6
10–90	38	60
>90	21	33
>97 (macrocephalic)	9	14

[a] Individuals counted as <3 or >97 are also counted as <10 or >90, respectively.

Table III. Pearson Correlations between Head Circumference and Cognitive and Clinical Variables

	Head circumference[a]
Age ($n = 63$)	.16
IQ	
Full scale ($n = 63$)	.01
Verbal ($n = 59$)	−.22
Nonverbal ($n = 59$)	.16
V-NV Difference Score[b] ($n = 59$)	−.38*
Language	
Vocabulary standard score[c] ($n = 63$)	−.17
Mean length of utterance ($n = 54$)	−.01
Executive Functions	
Working memory/inhibitory control ($n = 36$)	−.05
Planning ($n = 39$)	.27
ADOS symptom severity ($n = 63$)[d]	.12

[a] Calculated as a z-score based on normative data from Farkas (1994).
[b] Calculated by subtracting the DAS nonverbal standard score from the DAS verbal standard score.
[c] Mean of PPVT-III and EVT standard scores.
[d] Five children were administered ADOS Module 1, 23 were administered Module 2, and 35 were administered Module 3. ADOS module was partialed from the correlation to control for module-specific variance in ADOS scores.
* $p < .01$.

Table IV displays mean age, IQ, and standardized head circumference scores for each categorically defined V-NV profile group. The groups did not differ significantly in age [$F(2,56) = 2.32$, n.s.] An ANCOVA covarying verbal 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 [$F(2, 56) = 3.69$, $p < .05$]. 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 [$F(2,56) = 3.52$, $p < .05$], but not on head length

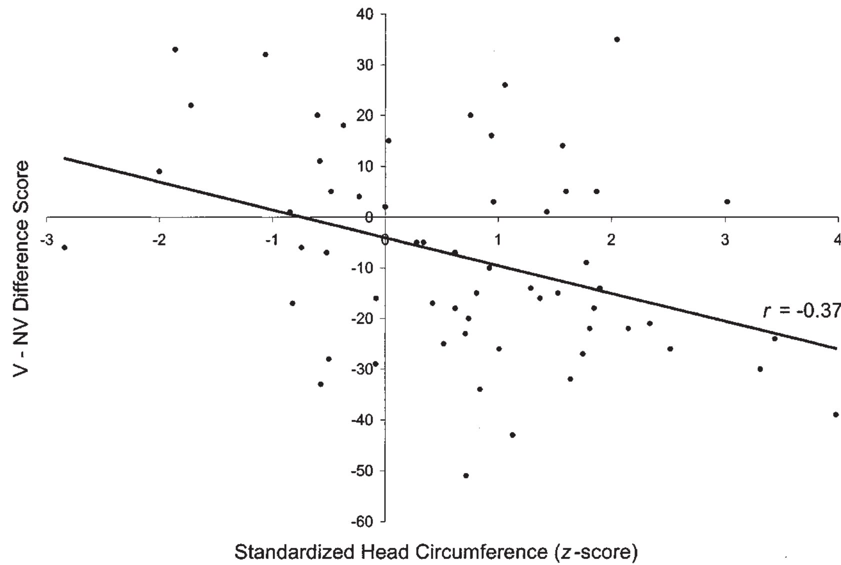

Fig. 1. V-NV difference score as a function of head circumference. Head circumference *z*-scores of 1.28 and 1.88 correspond to the 90th and 97th percentiles, respectively. AV-NV difference score of ±14 points is significant at the .05 level of probability.

[$F(2,56) = 1.75$, n.s.]. Table IV displays mean standardized head width and length for each V-NV group.

DISCUSSION

In this study, we identified a subgroup of children with autism who have unevenly developed nonverbal skills accompanied by unusually large head circumference. These findings converge with our previously reported findings linking discrepantly superior nonverbal skills to increased impairment in social functioning in autism (Joseph, Tager-Flusberg, & Lord, 2002) and provide further evidence that the V < NV profile may index an etiologically significant subtype of autism.

What might account for the co-occurrence between unevenly developed nonverbal abilities and large head size in autism? Unevenness in cognitive development and the presence of splinter skills have long been associated with autism (Frith, 1989; Happé, 1999), and nonverbal, visual-spatial processing skills have been identified as a relative cognitive strength for at least a

Table IV. Age, IQ Scores and Head Circumference as a Function of V-NV Discrepancy Group

	Verbal-nonverbal discrepancy group[a]					
	V < NV(n = 27)		V = NV (n = 21)		V> NV (n = 11)	
	M	*(SD)*	*M*	*(SD)*	*M*	*(SD)*
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)
Verbal IQ	72	(16.8)	74	(17.3)	89	(18.8)
Nonverbal IQ	97	(18.5)	75	(16.0)	66	(17.8)
Head circumference[b]	1.3	(1.2)	0.3	(1.4)	0.1	(1.3)
Head width	1.0	(1.1)	0.6	(0.8)	.01	(1.0)
Head length	0.3	(1.1)	−0.1	(0.9)	−0.2	(0.9)

[a] V-NV groupings were made on the basis of the minimum difference between scores required for significance at the .05 level of probability (Elliott, 1990).
[b] All head measurement figures are based on standardized z-scores.

subset of children with autism (Joseph *et al.,* in press; Lincoln, Courchesne, Allen, Hanson, & Ene, 1998). One possibility, suggested by the current findings, is that macrocephaly and unevenly developed nonverbal skills reflect the same underlying disturbance in neurocognitive development and organization. Although speculative, this hypothesis is consistent with evidence of increased brain volume, and particularly disproportionate growth of the posterior cerebral cortex in autism (Piven, Arndt, Bailey, & Andreasen, 1996), and with suggestions that isolated visual-perceptual skills in autism may be related to an excess of neurons and/or reduced cortical pruning and connectivity (Cohen, 1994; Happé, 1999). Further, evidence that an increase in head width is primarily responsible for enlarged head circumference in autism (Deutsch *et al.,* in press) would be consistent with enlargement of parieto-temporal cortex and is conceivably related to abnormal development of the visual-spatial skills mediated by these brain regions. More detailed, regional measurements of brain volume in macrocephalic children with autism will be necessary to determine if these phenomena are related.

A notable limitation of the current study is its exploratory nature. As a consequence, it will be especially important to assess the replicability of the association found between macrocephaly and unevenly developed nonverbal skills in an independent sample of similarly aged children with autism in whom the co-occurrence of these neurodevelopmental deviations may be most readily detectable. Use of cognitive assessment measures, such as the DAS, that are specifically designed to delineate differential patterns of cognitive strength and weakness will be most informative.

Further research is also needed to characterize the nature, causes, and significance of macrocephaly in autism. Two important variables to consider are rate of head growth and age of onset of macrocephaly in autism (Fombonne *et al.,* 1999; Lainhart *et al.,* 1997; see also Courchesne *et al.,* 2001). We have suggested that the V < NV profile in autism reflects abnormalities in neurocognitive development and organization, whereby different skills domains become increasingly uneven and dissociated in their functioning over time (Joseph *et al.,* in press). In the context of the current findings, a reasonable corollary hypothesis to investigate is whether the V < NV profile, which we did not find to be universally associated with macrocephaly, is specifically associated with an accelerating rate of head growth and/or later onset of macrocephaly. Such a finding would add further support to the distinctiveness of the V < NV profile in autism and provide further clues to its neurobiological genesis and underpinnings.

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