Head Size in Relation to Schizophrenia and Schizotypy

by William M. Grove, Boyd S. Lebow, and Carlota Medus

Abstract

Cranial breadth and length on DSM-III schizophrenic probands (n = 16) and their nonpsychotic siblings (n = 34) were measured using standard anthropometric calipers. Siblings were divided into those with and those without DSM-III schizotypal personality disorder based on Baron et al.'s Schedule for Schizotypal Personalities interview (1981). These siblings provide controls for prenatal and childhood nutritional status, which could affect head size, and for genetic contributors to head size. Contrary to previous reports (Andreasen et al. 1986; and Pearlson et al. 1989), in the present sample schizophrenic patients did not have smaller heads. The relationship between height and head size for schizophrenic subjects, schizotypal siblings, and nonschizotypal siblings was also examined. As in Andreasen et al. (1986), the regression slope of head size on height was lower in schizophrenic patients than in their siblings, but here this difference was not significant. The data do not support a conjectured relationship between small or dysmorphic head size and schizophrenia or schizotypy.

Andreasen et al. (1986) reported an unexpected finding regarding head size in schizophrenia. They planimetrically measured cranial size and brain area on transverse-plane magnetic resonance imaging (MRI) scan to see whether brain atrophy had occurred. Schizophrenic patients, especially males, had smaller heads than controls, who were mostly hospital employees. One possible explanation for such a finding is that a small head is caused by in utero or perinatal insult, which could potentially be a risk factor for later development of schizophrenia.

Another Andreasen finding, which received less attention, was that head size was not significantly related to height in schizophrenic patients. In normal controls, head size was strongly predicted by body size and height (see Gould 1981). The researchers reported a multiple R^2 of 0.39 for predicting cranial size from sex and height in controls, versus only 0.07 in schizophrenic patients, a significant difference (p < 0.05). (Although the analyses used sex and height as predictors, once height is included as a predictor, sex contributes no further predictability of head size and so can effectively be ignored.) The regression finding implies that schizophrenic patients' heads may be smaller or larger than one would expect from their height; in this sample, they were mostly smaller.

Green et al. (1989) reported an excess of smaller and larger head sizes in schizophrenic patients (especially female ones), buttressing the interpretation of the Andreasen data as essentially one of dysmorphic crania rather than microcephalia. Pearlson et al. (1989) confirmed the finding of smaller head size using computed tomography (CT) methods but did not report on the relationship of head size to height. Pearlson et al. also found a positive relationship between cranial size and high social class, which has been reported before and which led Stevens and Waldmon (1987) to suggest that the cranial- and brain-size differences reported by Andreasen were artifacts.

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of using poorly selected controls. Stevens and Waldmon suggested that socioeconomic differences between patients and controls could account for differences in head size, given data they presented showing a positive relationship in the general population between occupational status and head size. They implicated nutritional factors, stating that "there is little correlation between cranial size and intelligence" (p. 673), although actually the correlation is about the same size (0.30) as the one they showed between head size and occupational status (Van Valen 1974).

There are two problems with the Stevens and Waldmon (1987) hypothesis. First, it is probably quantitatively insufficient to account for the observed head size difference, which is large (about 1 SD in males). Second, Stevens and Waldmon’s alternative explanation was partly based on Andreassen’s schizophrenia sample having lower socioeconomic status (SES) than controls. If, however, SES leads to spurious head-size differences because nutritional differences are confounded with case-control status, schizophrenic patients should come from lower socioeconomic classes of origin. Poor nutrition brought on by recent poverty would not be expected to shrink one’s head. Epidemiological data on schizophrenia risk versus parental social class, however, suggest at most a very modest role for social class in schizophrenia (Kohn 1973).

One commonly used way to evaluate hypotheses about confounders like social class is to use an analysis of covariance (or, equivalently, a regression adjustment), with social class or some measure of it as a regressor or covariate. However, we explain in detail that such analyses, when applied to situations like these, may present grave logical and statistical problems (Grove and Waldman, submitted for publication). Therefore, we sought another way to investigate the head-size question. A useful way to explore this issue is to use controls matched to schizophrenic patients for SES. One potential control group so matched is the nonpsychotic siblings of schizophrenic patients. These siblings are excellent controls because they presumably have like status on many confounding variables: parental social class, quality of prenatal and neonatal nutrition, and maternal and child health care, to name a few.

In addition, such controls partly share the schizophrenic patient’s genes. The Stevens-Waldmon objection raises the question of environmental factors (nutrition). However, there is another interesting and testable hypothesis: that genetic factors contributing to risk for schizophrenia also contribute to small or disproportionate head size. From this alternate theory, one would predict two findings: (1) schizophrenic patients will show smaller head size than their nonpsychotic siblings, and (2) schizophrenic patients will show much the same regression of head size on height as their schizophrenic siblings. On an environmental insult model, the schizophrenic siblings should have smaller heads than their nonpsychotic siblings, both schizophrenic and nonpsychotic, and schizophrenic patients should show smaller regression of head size on height than either sibling group. These predictions were investigated using a sample of probands with schizophrenia and their schizophrenic and nonpsychotic siblings.

Methods

Probands. Probands were recruited from admissions and the outpatient clinic at the Psychiatry Department, University of Minnesota. Because of staffing limitations not every admission or clinic patient was screened, but whenever a new study intake was possible, the next consecutive admission and new outpatient diagnostic evaluation were screened. The sole exception was one proband who heard about the study and self-referred to the first author. There was no selection for having a "loaded" family history of schizophrenia. Inclusion criteria were (1) tentative DSM-III (American Psychiatric Association 1980) diagnosis of schizophrenia (to be confirmed by structured interview), (2) known identity of at least one living biological first-degree relative, and (3) age 18 or older (Minnesota legal consent age). Candidates were excluded if English was not their (and their relatives’) primary language, if their IQ measured lower than 70 or they had a chart diagnosis of mental retardation, or if they had current or past central nervous system disease (e.g., acquired immunodeficiency syndrome, epilepsy) or head injury with skull fracture or loss of consciousness. The study was described orally and in writing to each subject, and written informed consent was obtained. One proband’s head size was not measured before he or she left the hospital, leaving a net sample number of 16.

Relatives. For each consenting proband, a list of all liveborn first-degree relatives was compiled. With the proband’s permission, a best informant relative (usually the proband’s mother) was contacted to ensure complete and correct information about relatives’ identities and addresses. Relatives were contacted by mail, with telephone followup, to describe the study and invite the rel-
atives to participate. Relatives living within approximately a 250-mile radius of the Twin Cities were invited to the laboratory so that their heads could be measured; otherwise, they were invited to the laboratory only if they planned to be in the study area in the next 6 months or so.

Diagnoses. DSM-III Axis I diagnoses were assessed by trained raters (either the first author or an assistant trained by him) using a structured interview. Early probands and relatives were assessed with the Diagnostic Interview Schedule (DIS: Robins et al. 1981) chosen because it was at the time the only interview we knew that gave DSM-III diagnoses. However, its problems (it makes no systematic provision for including information from sources other than the interviewee and it does not allow for careful professional probing of ostensibly psychotic features) led us to begin using the Structured Clinical Interview for DSM-III-R (SCID; Spitzer et al. 1988) when it became available. We changed DSM-III-R diagnoses from SCID when necessary to make them conform to DSM-III, for comparability to DIS results. DSM-III schizotypal personality disorder (SPD) was assessed using the Schedule for Schizotypal Personalities (SSP; Baron et al. 1981). This interview has typically several items for each DSM-III symptom or sign. A symptom or sign is counted as present if at least one item in the symptom or sign group is rated at least 2.

Head Measurements. Head size was measured with anthropometric calipers according to standard methods (Weiner and Lourie 1969). Head length was measured from nasion to inion, and breadth was measured across the skull at the small concavities in each temple. The skin was compressed firmly but not to the point of subject discomfort. Measurements were recorded to the nearest millimeter. A cranial index was computed, which was simply the product of length and breadth. That this method ignored head-shape differences among subjects should not cause major problems because within-family controls were used. Height was also measured to the nearest inch (converted to centimeters), and sex was recorded.

Data Analysis. Because the cranial index had a highly skewed distribution (skewness > 2), which could affect regressions and the validity of significance tests, transformations were explored to reduce skewness. A transformation - 100000X/(cranial index)2.5 + 20 was empirically selected, which eliminated skewness while maintaining rank order of subjects. Schizophrenic patients were compared to their nonpsychotic siblings within families using a family × diagnosis analysis of covariance (ANCOVA) with height as the covariate. SPD siblings were compared to non-SPD siblings (excluding the schizophrenic proband) in the same way. The homogeneity of the regressions of cranial index on height was assessed by testing raw regression b-weights for equality.

Results

Probands. Twenty-two potential probands were asked to participate in the study: 18 agreed but 1 withdrew, yielding a net consent rate of 77 percent. Four of the probands (24%) were female. The age range was 22 to 53, with median and interquartile range of 29 (mean 31.24) and 24 to 35 (SD = 9.18), respectively. Age of onset ranged from 12 to 40, with median 23 and Q = 18.5 to 27. Because no proband had ever fully remitted since onset, durations of illness of current episode were the same as total durations of illness: median 7 years and Q = 3–10 years. DSM-III subtypes were distributed as follows: three paranoid, five disorganized, and nine undifferentiated. Of the nine patients with undifferentiated subtype, three had prominent persecutory delusions or hallucinations but did not meet criteria for paranoid subtype because flat affect was present. Head-size data were missing for one proband.

Relatives. In all, 102 liveborn first-degree relatives were identified. Of these, 9 were deceased. 1 was aged younger than 18, 1 could not be located, 3 lived outside the 250-mile radius. 25 were contacted but refused to participate, 2 agreed to participate but repeatedly failed to keep appointments, and 61 (71%) actually participated. Of these 61, 34 were siblings having available head measurements, of whom 18 (52%) were female; siblings' mean age was 31.1 ± 6.3; median age was 31 (Q = 27–35). Among relatives personally seen, three had a history of psychotic illness (one each with schizophrenia, major depressive disorder with mood-incongruent psychotic features, and major depressive disorder with mood-congruent psychotic features) and were not used for this report in order to ensure that the relatives were truly controls for our purposes. One sibling not seen and hence without head measurement had a family history-based diagnosis of chronic paranoid schizophrenia.
Head Size, Diagnosis, and Height.
Transformed cranial index, height in centimeters, and regression of the former on the latter (b-weight ± standard error of estimate) for schizophrenic probands, schizotypal nonpsychotic siblings, and nonschizotypal nonpsychotic siblings are shown in Table 1. The regression coefficients are those for a nested model (within-family) ANCOVA with height as the covariate. The group effect is proband versus non-proband status. The family mean effect is highly significant (F = 6.57; df = 15.13; p < 0.01), as one would expect, given the high heritability of body dimensions. The effect of proband status is not significant (F = 0.059; df = 1.00; p < 0.46). The difference between b-weights was tested by computing the F-test for the group (proband versus non-SPD sibling) × height interaction effect, and the result was not significant (F = 0.58; df = 1.13; p < 0.47). It is interesting nonetheless that the regression coefficient for probands is about one-fourth that of either sibling group; the nonsignificance of the difference may be due to low statistical power (see "Discussion").

Table 1. Head size in schizophrenics and nonpsychotic siblings

<table>
<thead>
<tr>
<th>Measure</th>
<th>Schizophrenic patients (n = 16)</th>
<th>Siblings SPD (n = 16)</th>
<th>Non-SPD (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranial index</td>
<td>7.47 (3.05)</td>
<td>6.68 (2.62)</td>
<td>6.32 (2.69)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>177.2 (6.78)</td>
<td>172.7 (3.00)</td>
<td>171.3 (10.89)</td>
</tr>
<tr>
<td>Regression on height</td>
<td>0.05 ± 0.22</td>
<td>0.25 ± 0.05</td>
<td>0.21 ± 0.05</td>
</tr>
</tbody>
</table>

Note.—SPD = schizotypal personality disorder.

Type II error. Power to detect a difference in standardized regression slopes between 0.26 for schizophrenic subjects and 0.62 (the square root of R² values in Andreasen's study) was in this study less than 0.7 (by interpolation in Table 3.2 of Cohen 1988); interaction effects of this kind are notoriously difficult to detect. We offer the findings, even though not significant, for consideration due to our essential replication of Andreasen's finding on the regression slope difference. The implication could be that disproportionately large or small head size is caused by genes other than those producing schizotypy or by environmental factors. Disproportionate head size would be an indirect index of vulnerability, in much the same way some investigators consider left-handedness in a family of right-handers to be a potential indicator of neurological insult.

Methodological differences could also account for our failure to replicate Andreasen. An essential difference between that study and ours is that Andreasen and co-workers used tracings of the inner table of the skull from transverse plane MRI scans. Doing so introduces two differences: first, brain size rather than head size is being measured; second, Andreasen allowed for skull-shape differences through planimetric measurement. By contrast, we simply found the area of a rectangle in which the skull would fit, ignoring skull shape. To the extent that subjects have similarly shaped heads (e.g., they are of the same race, same sex ratio), these two measurement methods should be in considerable, but by no means perfect, agreement.

The genetic model for small head size as a heritable schizotypy indicator is also not supported in that head size does not grade downward from nonschizotyp to schizotyp to schizophrenic. The data are consistent with an explanation emphasizing poor nutrition or inadequate prenatal health care. They are also consistent with the simplest hypothesis, namely that there is no small or disproportionate head-size phenomenon to be explained at all.

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