Neurological Soft Signs

Their Relationship to Psychiatric Disorder and Intelligence in Childhood and Adolescence

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• Sixty-three male and 27 female adolescents known to have had neurological soft signs at the age of 7 years were compared with controls with no soft signs at age 7. Adolescents with early soft signs had significantly lower IQs and were more likely to have a psychiatric disorder characterized by anxiety, withdrawal, and depression. All the girls and 80% (12/15) of the boys with an anxiety-withdrawal diagnosis showed early soft signs. There was no relationship between early soft signs and attention deficit or conduct disorders. Examination of the relative contributions of anxiety at age 7, IQ, and social and family disadvantage to later diagnosis showed that most of the variance was accounted for by soft signs independently of IQ. Soft signs and anxious dependent behavior at age 7 were strongly predictive of persistent psychiatric disorder characterized by anxiety and withdrawal.

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A *neurological soft sign* is a particular form of deviant performance on a motor or sensory test in the neurological status examination. The designation *soft* is usually taken to indicate that the person with the sign shows no other feature of a fixed or transient neurological lesion or disorder.[1] The clinical importance of soft signs lies not in any impairment of motor or sensory function associated with their presence, for there does not seem to be any, but in their value as an indicator of some CNS "factor" that might have causal or predictive value for associated psychological dysfunction and in particular learning and/or psychiatric abnormalities.

The relationship between soft signs and cognitive and psychiatric disturbance in children and adults has been reviewed previously.[2,3] Ideally, studies exploring this relationship should exclude patients with evidence of neurological disease; the examination of neurological and psychological features should be carried out "blind" to each other; the evaluations should be standardized and important biases in the population should be known. Findings that have emerged from the relatively few studies that fulfilled some, if not all, of these requirements are as follows: (1) soft signs are found more often in male pediatric psychiatric patients than in normal controls[4,5]; (2) within a group of disturbed children, soft signs are more common in those who are impulsive, distractable, dependent, and sloppy than in those who are not[6,7]; (3) within a group of adult psychiatric inpatients, soft signs occur more often in schizophrenics who have a history of social difficulties in childhood and in patients with labile mood[8]; and (4) in nonclinical pediatric populations signs are more common in boys and are associated with social immaturity, lack of motivation, lack of cooperativeness, and poor reading attainments.[9-11]

These findings suggest a relationship between soft signs and a variety of cognitive and psychiatric problems. However, the investigations from which they originate leave a number of questions unanswered. Studies on inpatients[8,12-14] may not have revealed a relationship between soft signs and a type of psychiatric disorder that did not usually lead to hospital admission. Studies on specialized clinical or institutional populations, such as hyperactive children or delinquents,[5-7,15-18] may not have revealed a relationship with other psychiatric conditions, and referral bias in such studies may lead to unrepresentative findings. The few studies in nonreferred populations have either been limited to the examination of a single neurological sign, such as the choreiform syndrome,[9,19] did not examine behavioral or emotional variables,[11] or examined only a limited set of behavioral variables so that a full psychiatric diagnosis could not be made.[10] Finally, because all previous studies are cross-sectional, they provide no information on the value of signs as a predictor of later or continuing psychiatric or cognitive disturbance.

To address some of these issues, we have carried out a controlled psychiatric and cognitive follow-up study on a

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nonreferred sample of adolescents whose soft-sign status was known at the age of 7 years. In a previous report on this group,[1] we noted a relationship between the presence of neurological soft signs and withdrawal-dependency behavior during psychological examination at age 7. The present report focuses on psychiatric disability, diagnosis, and IQ at the age of 17 years.

SUBJECTS AND METHODS

Subjects

Subjects were drawn from the 1962-1963 birth cohort of English-speaking boys and girls of the Columbia-Presbyterian Medical Center (CPMC), New York City, chapter of the Collaborative Perinatal Project (CPP).[20] The sample frame originally comprised every fifth woman registering during pregnancy at the CPMC prenatal clinic, excluding only declared adoption donors and women who received only brief prenatal care. Subjects in our sample were of the same racial background because as a group they had a higher prevalence of soft signs than the others. This finding was not generally true within the CPP population, and sex and ethnic rates overall did not differ consistently.[21] Index subjects (63 boys and 26 girls) had received a positive rating on any one of eight specific neurological signs on a neurological examination at age 7 but had been found free of any frank neurological disease or mental retardation (IQ <60). The same number of subjects of similar race and sex, but who had no evidence of abnormality at the seven-year neurological examination and who were closest in birth date to an index child were selected from the same CPP register to be controls. Subjects with and without signs at age 7 did not differ with respect to age at examination, cohort of inception, anomalous family situation, welfare dependency, poverty, or level of maternal education.

Six groups of signs were found represented in the group: awkwardness or poor coordination during finger-nose testing, finger pursuit, and complex fine-motor activities; dysdiadochokinesis, ie, the inability to perform rapid alternating movement of hands and feet in a smooth, fluent, and rhythmic fashion; mirror movements; tremor; dysgraphesthesia, ie, the inability to detect predisplayed symbols traced on the palmar surface when blindfolded; and astereognosis, ie, the incorrect identification of three-dimensional objects in the outstretched hand when blindfolded. The most frequently found signs were awkwardness in finger-nose touching, finger pursuit, and fine-motor activity. They were found alone or in combination with other signs in 37 of 60 boys and 12 of 26 girls. Dysdiadochokinesis was found alone or in combination in 31 of 60 boys and in 14 of 26 girls.

Boys and girls were examined sequentially, the girls being examined approximately one year after the boys. Data collection was completed for the girls before data from the boys were examined. Of the 126 boys selected for inclusion, 116 (92%) were examined when between the ages of 16 and 18 years. Of the 54 girls selected for inclusion, 48 (87%) were examined between the ages of 17 and 18 years. Losses from the original sample frame and the proportion of cases examined are shown in Table 1. Two control subjects could not be examined directly, but their parents were interviewed. Two male index subjects who were examined at age 17 were excluded from the sample after data collection was completed because early medical records suggested that frank neurological disorder (neurofibromatosis, microcephaly with intracranial calcification) had been present before age 7. A third subject with a simple tic at age 7 had been mistakenly included in the group with soft signs. These cases were excluded from the data analysis, but the number of controls was not reduced.

One female index subject who was examined at age 17 was excluded from the sample after data collection was completed because early records indicated that she had an IQ in the mentally retarded range.

Table 1.—Losses From Sample

	Boys		Girls	
	Soft Signs		Soft Signs	
	Present	Absent	Present	Absent
Eligible	63	63	27	27
Not located	. . .	3	. . .	. . .
Refused	2	3	1	5
Examined	61	57	26	22
Excluded after examination	3	. . .	1	. . .
Data base*	58 (97)	57 (90)	25 (96)	22 (81)

*Parenthetical numbers indicate percent of eligibles less late exclusions.

Procedures

Behavioral Assessment at Age 7.—Certain of the analyses presented subsequently use behavioral observations made by the examining psychologist during cognitive testing of 7-year-old subjects. Each child was rated on 15 different behaviors. The psychologist had no knowledge of the child's status on all other examinations. We constructed three a priori scales from the behavioral ratings assigned to all (N = 440) children in the 1962-1963 CPP birth cohort to denote (1) hyperactivity, (2) aggression, and (3) dependency-withdrawal.[1] Internal reliability as indicated by Cronbach's α-value for the dependency-withdrawal scale used in this report was .71.

Neurological Assessment at Age 7.—The neurological examinations at age 7 were conducted in 1969 and 1970 according to the National Collaborative Perinatal Project protocol (PED-76). Board-certified pediatricians, under the supervision of a senior certified pediatric neurologist, performed all examinations without knowledge of the children's medical history. The examination included tests for 18 neurological soft signs. Test-retest agreement was determined in a subsample[21] and was found to be 85% in the most frequently diagnosed group of signs (poor coordination). It is probable that there were substantial threshold differences in different collaborating centers, and they were reflected in different prevalence rates. The prevalence of signs at CPMC was the highest of all participating centers, suggesting that the identification threshold was probably the lowest. In view of the uncertainties about relevant threshold levels the bias toward overinclusiveness was believed to be an advantage for the present study.

Psychiatric Assessment at Age 17.—The psychiatric evaluation of the adolescent subjects included a semistructured interview with the adolescent compiled primarily from existing instruments of demonstrated reliability. These instruments included portions of the Schedule for Affective Disorders and Schizophrenia[22] to assess affective and psychotic symptoms, elements from the interview developed by Rutter and Graham[23] to assess social and family relationships and antisocial behavior, and a number of new elements that were designed to elicit symptoms required to assign the range of diagnoses represented in *DSM-III*. Developmental lags (axis II) were not coded because formal tests would allow us to assign precise values to academic attainments and IQ. At the end of the interview, the interviewer rated the adolescent's overall functioning on the Global Assessment Scale (GAS).[24] Persons with a score of less than 70 on the GAS, a level designated as indicating functional impairment from psychiatric symptoms, were assigned a psychiatric diagnosis. Interrater reliability around this threshold value was satisfactory. In a subsample of nine subjects, we obtained 79% agreement between six to nine raters on whether the subject should be assigned a GAS score greater or less than 70. Other methodological properties of this procedure have been described more fully elsewhere.[3]

A semistructured interview with a parent informant (usually the mother) adapted from that described by Rutter and Brown[25] was used to obtain demographic data and additional information on the adolescent's recent behavior. The interview also elicited information concerning educational and family history and the parents' medical, social, and marital history. The General Well-Being Scale[26] was incorporated in the assessment to determine the presence of psychiatric symptoms in the parent. As at the end of the adolescent interview, the interviewer used the information obtained from the parent to provide a GAS rating of the adolescent's functioning.

Table 2.—Soft Signs at Age 7 and IQ at Age 17

IQ Measures Tested at Age 17*	No Signs at Age 7	1 Sign at Age 7	≥ 2 Signs at Age 7	F	P
Boys					
No. of subjects	54	29	29	...	...
Full-scale WISC IQ, $\bar{X}$	94.4	91.0	85.8	6.46	.01
Verbal IQ, $\bar{X}$	94.2	91.6	87.5	3.61	.05
Performance IQ, $\bar{X}$	95.4	91.4	85.6	7.15	.001
IQ ≤85, %	22	31	41	3.38†	NS
Girls					
No. of subjects	21	18	3	...	...
Full-scale WISC IQ, $\bar{X}$	98.8	96.4	88.3	...	...
Verbal IQ, $\bar{X}$	99.8	96.3	90.0	...	...
Performance IQ, $\bar{X}$	99.4	97.4	88.0	...	...
IQ ≤85, %	10	17	33	...	...

*WISC indicates Wechsler Intelligence Scale for Children.
†χ^2 value.

Conners' Teachers' Questionnaire (CTQ)[27] was completed by each of three high school teachers—the adolescent's most recent mathematics, English and social studies teachers.

Different interviewers, with no knowledge of the soft sign status of the subjects, interviewed different members of the adolescent-informant pair. Data from adolescent, parent, and teachers were used to arrive at a final diagnosis.

If a subject was assigned a GAS rating of 70 or less by the interviewer who examined either the adolescent or the informant or if only one interview was available and the GAS rating was lower than 75, ie, at a slightly higher threshold, a summary of relevant information was reviewed by a committee of two psychiatrists (D.S. and P.T.) and one psychologist (P.O.C. or I.S.) with no knowledge of the adolescent's soft-sign status. An overall GAS rating and as many *DSM-III* axis I diagnoses as appropriate were then assigned by agreement. Exclusionary, hierarchical rules were not applied, and it was possible, for example, for a subject to be assigned diagnoses of both conduct disorder and attention deficit disorder or conduct disorder and affective disorder. Few constraints were placed on the assignment of second or further diagnoses. One effect of this method would be to lessen any disproportionate weight that might have been carried by the senior committee member's diagnostic views.

At the end of the diagnostic process, a list of assigned *DSM-III* diagnoses was drawn up, without knowledge of their distribution between groups or within subjects. The diagnoses were then classified into five supraordinate categories: affective disorders, conduct disorders, anxiety-withdrawal disorders, substance abuse, and others. The grouping of anxiety and withdrawal diagnoses is customary in child psychiatric nosology under a general rubric of "childhood emotional disorder."[28]

Subjects not reviewed by the committee (because the GAS ratings assigned by both interviewers were in the normal range) were assigned a final GAS rating that was the arithmetic mean of the two interviewers' GAS ratings.

Neurological Assessment at Age 17.—The neurological examination was designed to reevaluate the status of the subjects using categories and methods broadly comparable to those used at age 7 (S. Q. Shafer, C. J. Stokman, D. Shaffer, et al, unpublished data, 1984). Its interrater and test-retest reliability have been described elsewhere (C. J. Stokman, S. Q. Shafer, D. Shaffer, et al, unpublished data, 1984).

Assessment of IQ at Age 17.—A broad battery of cognitive tests, including the Wechsler Adult Intelligence Scale (WAIS),[29] was administered to 112 (97%) of the 115 boys and to 42 (81%) of the 47 girls examined.

The psychiatric, neurological, and cognitive examinations all took place on one day; all subjects were tested first on the cognitive battery. The parent informant was interviewed on the same day or as close as possible to the day that his or her child was seen. When subjects were seen out of town, whether in their homes or in prison, the scheduling order was, of necessity, more flexible, and followed institutional or travel schedules. The CTQ forms were sent to schools at about the time the adolescent interview was to be conducted.

RESULTS

Intelligence

The relationship between IQ (at age 17) and the number of soft signs present at age 7 is presented in Table 2. Within the male sample, significant between-group differences were found in mean full-scale, verbal, and performance IQs, the group with no signs having the highest mean IQ and the group with two or more signs having the lowest mean IQ. The group with one sign only had intermediate values. Scheffe's post hoc test indicated that the group with no signs performed significantly better than the group with two or more signs on each of the IQ measures ($P<.05$). More of the subjects with soft signs had an IQ of less than 85. Within the smaller female sample, there were no significant between-group differences, although there was a trend similar to that found in the male sample.

Psychiatric Disorder

Fifty-one boys and 15 girls were assigned a GAS score of 70 or less and were considered for a psychiatric diagnosis. The 27 different *DSM-III* diagnoses assigned were grouped into five supraordinate categories. The distribution of these across the different sexes and across index and control groups is presented in Table 3.

Compared with the same-sex controls, significantly more male, but not female, adolescents who had soft signs at age 7 had a psychiatric disorder at age 17. There was an apparently linear relationship, with disorder being highest among boys with two or more signs, least for those with no signs, and at an intermediate value among those with only one sign (see Table 4).

When specific diagnoses were examined (see Tables 3 and 4), significant soft-sign relationships were found for the anxiety-withdrawal disorders in both sexes and for affective disorders only in boys. All six girls and 12 of the 15 boys with an anxiety-withdrawal diagnosis and 13 of the 20 boys with an affective diagnosis had had soft signs at age 7. The relationship between number of signs and rate of anxiety-withdrawal disorder in both male and female samples was found to be linear.[30] There were no significant differences in the prevalence of conduct disorders in the two groups. There were four adolescents with attention deficit disorder who were included in the group with conduct disorder; two of these were found to have had signs and two were found to be controls. The one adolescent with schizophrenia and the one with schizoaffective disorder had both had soft signs at age 7.

It is possible that we selected too conservative a threshold by only assigning diagnoses to adolescents with a GAS score under 70 and that the relationship between soft signs and general functioning was present also within subjects with a GAS score of 71 and over, between children with no, one, or more soft signs ($F=.26$), although given the restricted GAS range in this limited sample, this test may have been relatively insensitive.

Neurological signs at age 7 were grouped into those involving disorders of coordination (finger-nose movements, finger pursuit, and dysdiadochokinesis), involuntary movements (including synkinesis or mirror movements), and sensory signs (dysgraphesthesia and astereognosis). Poor coordination signs were found to be overrepresented in the anxiety-withdrawal group. Of the 21 subjects (both sexes) with an anxiety-withdrawal diagnosis, 17 (81%) had had a sign reflecting a disorder of coordination at age 7, three of these cases having both a coordination sign and a sign from another group. This result compares with poor coordination signs in 45 (37%) of 121 adolescents with no disorder or a different type of disorder ($\chi^2=12.21$, $df=1$, $P<.001$). The prevalence of poor coordination signs was not significantly different between the no-disorder (29/96 [30%]), affective disorder (11/27 [41%]), and conduct disorder groups (14/33 [42%]). There were no differences in the prevalence of the other groups of signs between adolescents with

Table 3.—Distribution and Grouping of *DSM-III* Diagnoses

DSM-III Diagnosis at Age 17	Signs Present at Age 7		Signs Absent at Age 7	
	M	F	M	F
Conduct				
312.00 Conduct disorder, undersocialized, aggressive	1	...	1	...
312.21 Conduct disorder, socialized, nonaggressive	8	1	6	1
312.23 Conduct disorder, socialized, aggressive	3	...	3	1
313.81 Oppositional disorder	4	...	1	...
314.01 Attention deficit disorder, with hyperactivity	2	...	1	...
314.80 Attention deficit disorder, residual	...	...	1	...
Affective				
295.70 Schizoaffective disorder	1	...	...	...
296.20 Major depression, single episode, unspecified	1	...	1	1
296.22 Major depression, single episode, without melancholia	2	...	...	...
296.23 Major depression, single episode, with melancholia	...	...	...	1
296.32 Major depression, recurrent, with melancholia	1	...	...	...
296.36 Major depression, recurrent, in remission	2	...	...	...
296.56 Bipolar disorder depressed, in remission	...	...	1	...
296.82 Atypical depression	1	1	2	...
300.40 Dysthymic disorder	3	1	2	1
301.13 Cyclothymic disorder	...	1	...	1
309.00 Adjustment disorder with depressed mood	2	...	1	...
Anxiety-withdrawal				
300.00 Atypical anxiety disorder	...	...	1	...
300.29 Simple phobia	...	1	...	...
301.22 Schizotypal personality disorder	1	...	...	...
309.21 Separation anxiety disorder	1	...	...	...
313.00 Overanxious disorder	8	4	1	...
313.21 Avoidant disorder of adolescence	2	...	1	...
313.22 Schizoid disorder	...	1	...	...
Substance abuse				
305.01 Alcohol abuse, continuous use	1	...	...	...
305.02 Alcohol abuse, episodic use	...	1	...	...
305.21 Cannabis abuse, continuous use	1	...	4	1
305.91 Other, mixed substance abuse, continuous use	1	...	...	1
Psychotic disorder				
295.32 Schizophrenia, paranoid type, chronic	1	...	...	...
Total	**47**	**11**	**27**	**8**

and without disorder and between adolescents with different types of disorders.

Possible Confounding Effects of IQ

Because soft-sign status at age 7 is related to both IQ and psychiatric disorder, it was possible that the excess of psychiatric disorder in the index group was a function of IQ. However, when the prevalence of different psychiatric diagnoses was examined in boys with an IQ greater than or equal to 85 (N=85) a similar association was found. Of the 47 boys with normal intelligence and no disorder, 60% had no signs, 26% had one sign, and 15% had two or more signs. By contrast, of the nine boys with an anxiety-withdrawal diagnosis only one (11%) was found to be free of signs, two (26%) were found to have one sign, and five (56%) were found to have two or more signs. Of the 16 boys with an affective diagnosis, seven (16%) had no signs, two (10%) had one sign, and seven (41%) had two or more signs ($\chi^2=5.92$, $df=2$, $P<.10$). There was no excess of soft signs in the children with normal IQs who had a conduct disorder.

The association between early signs and affective and anxiety diagnoses could still be confounded by the association between signs and IQ, for, within the sample of boys with an IQ greater than or equal to 85, IQ and GAS score remain positively correlated ($r=.24$, $P<.05$). However, correlational and regression analyses reported subsequently suggest that the relationship between anxiety and affective disorders and the number of early signs is independent of IQ.

Predictors of Psychiatric Disorder

Social Disadvantage.—Biological factors may show their effect regardless of external conditions or they might interact with environmental influences to modify the person's vulnerability. To investigate this possibility the sample was rated for different degrees of family and social disadvantage. A scale was constructed, a priori, for use in a multivariate analysis (see below) without knowledge of its distribution between index and control groups. It included 12 items assessed during the interview with the parent that are commonly held to be associated with child psychiatric disturbance and that could reasonably be assumed to be external to the child's neurological state. They included being a single parent, four or more siblings; incomplete parental education, either parent having had psychiatric treatment or a police record, welfare dependency, and low income and evidence of marital dissatisfaction.

Table 4.—Soft Signs at Age 7 and Psychiatric Diagnosis at Age 17

Diagnosis* at Age 17	No. (%) of Subjects: No Signs at Age 7	1 Sign at Age 7	≥2 Signs at Age 7	χ^2	P†
		Boys			
No. of subjects	57	29	29	...	...
Any disorder (GAS ≤70)	20 (35)	13 (45)	18 (62)	5.67	.05
Affective disorder	7 (12)	3 (10)	10 (34)	8.75‡	.01
Anxiety-withdrawal disorder	3 (5)	4 (14)	8 (28)	10.05§	.01
Substance abuse	4 (7)	2 (7)	1 (3)	...	...
Conduct disorder	13 (23)	9 (31)	8 (28)	...	...
No disorder	37 (58)	16 (25)	11 (17)	...	...
		Girls			
No. of subjects	22	20	5	...	...
Any disorder (GAS ≤70)	5 (23)	8 (40)	2 (40)	...	...
Affective disorder	4 (18)	3 (15)	0 (0)	...	...
Anxiety-withdrawal disorder	0 (0)	4 (20)	2 (40)	6.41 ‖	.05
Substance abuse	2 (9)	1 (5)	0 (0)	...	...
Conduct disorder	2 (9)	1 (5)	0 (0)	...	...
No disorder	17 (53)	12 (38)	3 (9)	...	...

*GAS indicates Global Assessment Scale.
†Statistical tests are one-tailed.
‡One cell had an expected value less than 5.0.
§Two cells had expected values less than 5.0.
‖Four cells had expected values less than 5.0.

Table 5.—Relationship Between IQ, Number of Early Signs, Social Disadvantage, and Psychiatric Impairment

Subjects	No.	Predictor	R^2	R^2 Increase	F*	(P)
		Boys				
All subjects	105	Social disadvantage	.08	.08	7.74	(<.01)
		Signs	.16	.08	6.23	(<.01)
Anxiety/no disorder	71	Signs	.25	.25	...	
		Early anxiety	.28	.03	...	
		Signs + early anxiety†	.31	.01	5.84	(<.05)
Affective/no disorder	76	Signs	.10	.10	9.60	(<.01)
		Social disadvantage	.15	.05	5.15	(<.05)
Conduct/no disorder	85	IQ	.10	.10	4.03	(<.05)
		Social disadvantage	.15	.15	4.34	(<.05)
		Girls				
All subjects	40	None‡	...	...	...	
Anxiety/no disorder	31	Signs	.24	.24	7.04	(<.05)
		IQ	.31	.07	3.05	(<.10)
		Social disadvantage	.37	.06	2.82	(<.11)
Affective/no disorder	33	None‡	...	...	...	
Conduct/no disorder	...	NC§	...	...	...	

*F statistics were computed when all four risk factors (early signs, social disadvantage, IQ, and early anxiety) were in the regression equations.
†Entering the signs and early anxiety product term after both signs and early anxiety have been entered reduced from significant to nonsignificant levels the β-weight of each of the factors.
‡No significant prediction.
§These regression analyses were not computed (NC) because too few girls (three) had a conduct disorder.

Values were range-standardized, and a mean disadvantage score was obtained for all except two subjects for whom most disadvantage data were missing. The standardized α-coefficients of this scale indicated satisfactory internal reliability for both boys (.64) and girls (.67).

Anxiety at Age 7.—We were also interested to see the extent to which anxiety recorded by the examining psychologist at age 7 (who had no knowledge of the child's neurological status) was predictive of later anxiety status. To study this aspect we used an item scale (see Shaffer et al[1]) derived from the psychologist's observations of the child's behavior during psychological testing at age 7 (fearful, shy, unconfident, unreactive, suggestible, rigid, only answers directed questions, withdraws in response to frustration, dependent, perseverative, and inactive). The internal reliability of this scale was satisfactory (standardized α-coefficient, .71).

This scale was included among several complementary sets of analyses carried out to examine the independent contribution of

Table 6.—Persistence of Signs and IQ in Relation to Soft Signs and Anxiety at Age 7

Variable	Signs and Anxiety at Age 7	Signs With No Anxiety at Age 7	Anxiety With No Signs at Age 7	No Signs or Anxiety at Age 7	Statistic (3)	P
Signs						
Boys						
No. of subjects	21	33	15	39	...	...
% with signs at age 17	67	58	27	31	$\chi^2 = 11.30$ (3 *df*)	.01
Girls						
No. of subjects	4	21	2	20	...	...
% with signs at age 17	50	29	50	25	...	...
IQ						
Boys						
No. of subjects	22	34	17	43	...	...
Mean IQ at age 7	82.4	95.3	93.7	98.5	$F = 10.87$ (3,112 *df*)	.001
Girls						
No. of subjects	4	22	2	25	...	...
Mean IQ at age 7	88.8	100.4	97.5	98.6	...	...

Table 7.—Risk for an Anxiety-Withdrawal Diagnosis (AWD) at Age 17

Findings at Age 7	AWD Present at Age 17	AWD Absent at Age 17	Odds Ratio	P*
Neither signs nor early anxiety	2	58	1.0	...
1 sign, no early anxiety	4	32	3.6	NS
≥2 signs, no early anxiety	3	16	5.4	.10
Any sign, no anxiety	7	48	4.2	.10
No signs and early anxiety	1	17	1.7	NS
1 sign and early anxiety	4	8	14.0	.01
≥2 signs and early anxiety	6	7	24.9	.001
Any sign with early anxiety	10	15	19.3	.001

*All tests were one-tailed and used Yates' correction.

IQ, current environmental disadvantage, and early anxiety-withdrawal behavior to psychiatric diagnosis at age 17.

Multivariate Analyses.—Because of a pattern of intercorrelations between IQ, social disadvantage, soft signs, and early anxiety-withdrawal (the predictor variables), least-squares regression analyses were conducted to determine their relative contribution to the different psychiatric disorders. Hierarchical regression analyses were conducted to assess the explanatory power of each predictor variable while controlling for the effects of the other three. In addition, stepwise regression analyses were conducted to highlight the amount of variance in GAS rating explained by each predictor (Table 5).

The risk factors that explained the greatest amount of variance differed according to how the samples were constituted. In the complete male sample, regardless of diagnosis, number of early signs and social disadvantage explained most variance; however, within the group that excluded all disturbed adolescents except those showing an anxiety-withdrawal disorder, the number of early signs was found to be the single best predictor of GAS value, with early anxiety independently contributing to a lesser but still significant degree to the explained variance. Within the group that excluded all disturbed adolescents except those showing affective disorders, neurological signs were also the best single predictor of GAS, although they explained much less variance than for anxiety-withdrawal diagnosis. In the male group that excluded all disturbed children except those with a conduct disorder, IQ and social disadvantage were the best predictors. No predictors were found in the complete female sample or in the group consisting of girls excluding all disturbed children except those with an affective disorder; however, number of early signs was the best predictor of GAS when all but anxiety-withdrawal disorders were excluded.

Additional regression analyses were undertaken to detect the presence of interaction effects. They confirmed the presence of an early-anxiety-by-signs interaction in boys but not in girls.

Because multiple diagnoses are related to more severe disorder, lower GAS ratings in the anxious-withdrawn subjects may not reflect an increased number of symptoms (and by implication severity of disorder) used to make an anxiety-withdrawal diagnosis. This finding would affect the interpretation of the regression analyses. To address this possibility, additional regression analyses were undertaken with GAS values appropriately adjusted. These analyses identified the same best predictors as the first set of analyses. Another approach to this analytic problem is to treat disorder as a categorical variable. Linear regression techniques were applied in the male subjects using dichotomous dependent variables[31] (anxiety-withdrawal/no disorder; affective/no disorder; and conduct/no disorder). These regressions identified the same best predictors as the other analyses. Linear regression techniques were not applied to disorders among the girls, because their prevalence fell far short of the 20% criterion needed to conduct such analyses.

Anxiety as a Cause of Signs.—A number of the findings reported herein suggest that the relationship between neurological soft signs present at age 7 and a later anxiety-withdrawal disorder is a real one. However, the direction of the association is not clear. It is possible that 7-year-old children who were anxious behaved in an aberrant way during neurological testing and that could have biased the examining clinician who might then rate the child as having a neurological soft sign. A group defined at age 7 as being both anxious and having signs would therefore have included cases in which soft signs were misdiagnosed as present (for had they not been anxious during testing they might have been rated as showing no signs). Because anxiety and withdrawal at ages 7 and 17 are related (excluding all disturbed subjects except those with an anxiety withdrawal diagnosis; 9/29 [31%]) the boys who at age 7 scored in the top quartile on the anxiety scale had an anxiety-withdrawal diagnosis at age 17, compared with only five (10%) of 48 of those who scored below the top quartile [$\chi^2 = 3.87$, $df = 1$, $P < .05$]), this factor could have influenced our findings at age 17.

If the group showing soft signs and anxiety included a number of cases in which the soft signs were designated as present we would expect it to differ from the group showing soft signs but no anxiety and to more closely resemble one of the groups with no soft signs. The children who were rated as having soft signs and no anxiety

would be expected to include only children with true soft signs and might therefore be expected to be the most deviant. To examine this possibility we compared these groups on two indexes that we had found to be associated with soft signs and in which an association had also been reported in the literature, ie, the persistence of signs across time and low IQ (Table 6).

Contrary to what we would predict if signs were an artifact of test anxiety, we found that the presence of both signs and anxiety at age 7 is associated with greater sign persistence for boys (there were too few anxious girls at age 7 for us to extend the analysis to girls). Furthermore, a comparison between the two groups with no soft signs shows no effect of anxiety alone. The findings with respect to IQ are similar, the group with both anxiety and signs was the most deviant (ie, had the lowest IQ) at age 17. Scheffe's post hoc tests indicated that the group with both soft signs and anxiety differed significantly from the other groups. This difference is unlikely to be due to the effect of anxiety symptoms on psychological test performance because the group with no soft signs with anxiety had a mean IQ score that was similar to the group with neither signs nor anxiety. On the basis of these findings, we conclude that anxiety is unlikely to have led to the false detection of signs during the neurological examination.

Early Anxiety and Signs as Risk Factors for Later Anxiety-Withdrawal Disorder.—Table 7 presents estimates of relative risk. The statistic used is the odds ratio, which indicates the degree of association between the risk factors and the presence of an age-17 anxiety-withdrawal diagnosis in the complete sample of both sexes. In the absence of signs, the presence of anxiety at age 7 did not significantly increase risk for an anxiety-withdrawal diagnosis at 17 (row 1 *v* row 4). By contrast, the presence of any sign even in the absence of early anxiety (rows 2 and 3 *v* row 1) was associated with a moderately increased risk of incurring an anxiety-withdrawal diagnosis ($\chi_y^2 = 2.33$, $df = 1$, $P < .10$ [one-tailed]). The presence of any sign along with early anxiety was associated with a considerably enhanced risk for an anxiety-withdrawal diagnosis at age 17 (rows 2 and 3 *v* rows 5 and 6) ($\chi_y^2 = 6.10$, $P < .01$ [one-tailed]).

In summary, the presence of early soft signs was associated with increased risk for a diagnosis of an anxiety-withdrawal disorder, especially in the presence of early anxiety. The pattern of findings is broadly consistent with the results of the regression analyses, which revealed a sign by early anxiety interaction.

COMMENT

Findings and Their Implications

We have described a follow-up study into the relationship between neurological soft signs present in middle childhood and psychiatric and cognitive states in adolescence. The presence of certain neurological signs (those involving impairment in motor coordination) at age 7 was predictive of psychiatric disturbance at age 17 and in particular of affective and anxiety disorders in boys and anxiety disorders in girls. The relationship is a clear one; all of the girls and 80% (12/15) of the boys who had anxiety diagnosed at age 17 had neurological soft signs at age 7. Although in this sample soft signs are virtually a necessary condition for the manifestation of anxiety disturbance in adolescence, they are not sufficient. A large majority of children with soft signs did not go on to have an anxiety or affective diagnosis in later adolescence. However, a reanalysis of data obtained from the same sample at age 7 suggests that predictive specificity can be increased by taking both the child's neurological and mental status into account. Of the children who had soft signs and who also displayed anxious dependent behavior during psychological testing at age 7, just under half would go on to show anxiety or affective disturbance in later adolescence.

Anxiety disorders in adolescence were unrelated to disadvantageous environmental factors. In contrast, antisocial disorder was unrelated to early neurological status except through a confounding relationship with IQ, but could be predicted from environmental disadvantage.

A number of implications emerge from these findings:

1. Psychiatric impairment in adolescence that is characterized by anxiety and social withdrawal (and in boys' affective disorder) has often been present since early childhood.
2. Anxious withdrawn behavior in adolescence may be predicted in early to middle childhood. This finding may have implications for prevention.
3. There is a relationship between anxiety states and such organic factors as are reflected by poor coordination shown during a neurological status examination.
4. The anxiety disorders that were related to neurological signs showed a variety of clinical features. However, none of the adolescents had panic disorders. This relationship of different anxiety syndromes to a common factor fails to provide empirical justification for a phenomenologically based subclassification of anxiety disorders.
5. The study provides no basis for linking soft signs to hyperkinesis, as is often formulated in the traditional minimal brain dysfunction syndrome, or to aggressive or antisocial behavior, except through their effect on IQ.

Reliability and Validity of the Findings

There are a number of reasons for believing in the integrity of the findings that have been reported:

1. The original sample frame was a nonclinical one and was unselected for any of the dependent variables of interest. Assignment bias is therefore unlikely to have led to unrepresentative findings.
2. Because the completion rate for the follow-up was high, around 90% for both samples, and the sample included all youths who were institutionalized or hospitalized, significant bias in either the residual or the unexamined samples is unlikely to account for the findings.
3. The study was carried out by examiners who had no knowledge of the subjects' antecedent status, and the findings were unpredicted by the investigators.
4. Standardized measures of established reliability were used for all elements of the study.
5. We found similar results in two independent samples: boys and girls. The examination of the girls was carried out as a separate exercise by a largely different team of research workers before the findings from the male sample were available. The parallel findings from each sex can therefore be regarded as replicating each other with similar instruments and research methods and diagnostic criteria.
6. The findings from the examination of the 17-year-olds are consistent with the findings previously reported among 7-year-olds.[1] However, the observations among the 7-year-olds were made on a much larger (N = 537) but nevertheless overlapping sample with a different set of behavioral data from a more restricted observational setting. The similarity underlines the consistency and hence probable validity of the findings; the difference in the two samples, their ages and the methods of investigation, speak to their robustness.
7. By and large there is a linear relationship between the antecedent and the dependent variables, ie, the difference between sign-free controls and children with one sign are intermediate to the difference between controls and adolescents with more than one sign. This finding would support a causal relationship.
8. The findings are consistent when both more sensitive, multivariate and more conservative, categorical statistical methods are used.

The methodological strengths listed previously sug-

gested that the association was a real one, but we attempted to disprove it in a number of ways. Children with soft signs had a lower IQ, and it was possible that performance during the neurological examination was determined by IQ. This interaction could either be at a superficial level, through a failure to understand or execute the examination instructions, or because the relationship between low IQ and poor academic performance leads to an anxiety or affective disturbance through the cumulative effect of repeated failures at school. However, we found the relationship between soft signs and anxiety and affective diagnoses to hold for children whose IQ scores were in the normal range. Furthermore, when multivariate statistics were applied to partial out the effects of IQ, we found signs remained strongly associated with anxiety-withdrawal diagnoses.

Another possible explanation is that anxious children show neurological signs on examination not because of any underlying neurological abnormality but because test anxiety interferes with an essentially behavioral performance. We used an indirect strategy to explore this possibility, hypothesizing that the group of children who were both anxious and who were recorded as having neurological signs at age 7 would include a number who would have been found to be neurologically normal had they not been nervous at the time of their examination. If this were so, then that group should resemble the neurologically normal children and should show fewer deviations or abnormalities than the children who had signs but who were not anxious at the time of examination (for whom test anxiety could not be invoked as an explanation). However, when we made these comparisons, we found that the reverse was true. The children who were both anxious and who had neurological abnormalities at age 7 proved to be the most deviant group in two indexes that we found to be generally associated with neurological signs, ie, the persistence of signs across childhood into adolescence and low IQ. We also found that neurological status at age 7 was more strongly predictive of psychiatric status at age 17 than was neurological status at age 17 (unpublished findings). This result contradicts the hypothesis that the findings are artifactual, because if anxiety mediated the outcomes of both the psychiatric and the neurological examinations, we would expect anxiety and signs to be most strongly associated when the examinations were carried out at the same time, at age 17.

In spite of these arguments for the validity of the findings, we cannot claim that this study exhaustively describes the nature of the relationship between neuromotor performance and psychiatric disorder. The range of neurological signs represented in the sample is restricted and a number of soft signs were either not present at all in our sample, were not sought, or were found with such a low frequency that they could not be subjected to statistical analysis. Somewhat similar considerations apply to the psychiatric evaluation. Although the examination was comprehensive, drew information from multiple sources, and was designed to determine the presence of most *DSM-III* diagnoses, some psychiatric diagnoses are so rare that they are unlikely to occur in a sample of this size. Thus, there was only one case of schizophrenia (a youth who had signs), and there were no autistic children or children with uncontrollable or extremely violent outbursts. The relationship between those disorders and signs remains unexplored.

The study was carried out in a racially homogeneous and to a large extent (but by no means universally so) underprivileged population. It could be held that the findings will not generalize to other ethnic groups, but the absence of any interaction between a social-environmental scale and soft signs and anxiety makes it unlikely that findings would differ in a more advantaged population. The social disadvantage scale applied to this population had satisfactory internal reliability and it appeared to have a measure of construct validity since it was a good predictor of conduct disorder. We therefore believe that the scale had sufficient variability to elicit an interaction if one were present.

Finally, there is evidence that the original investigators of the CCPP sample applied a somewhat lower threshold in determining the presence of neurological soft signs than did investigators at other centers.[21] Although we know of no directly comparable studies carried out heretofore, this factor would need to be borne in mind in any further replication because coordination difficulties of the kind identified might fall below the threshold habitually applied by clinicians elsewhere.

Compatibility With Other Research

The literature on the continuity of anxious-withdrawn behavior from early childhood is sparse, but can be read as supporting our findings. In studies on a normal population in the Berkeley Growth Study,[32] anxious-withdrawn behaviors in young boys and excessive dependency in girls were predictive of later psychopathologic findings, although the nature of the adult disturbance was not specified. Gersten et al[33] conducted a five-year follow-up study of children and adolescents first investigated in a population-based sample of Manhattan households and noted the persistence of anxiety symptoms from adolescence into early adulthood but not from early childhood. Both of these studies report moderate continuity; however, neither have taken neurological status into account as a factor in determining the stability of the symptom complexes.

In a follow-back study of adult patients who had not necessarily received prior treatment, Sylvester et al[34] reported that a majority with anxiety symptoms could date the onset of symptoms back to childhood. Follow-up studies on treated patients[35-40] in general indicate that anxious-withdrawn behavior in early childhood has, at least by comparison with the conduct disorders of childhood, a good prognosis. Although this finding would suggest that early identification is likely to be useful for prevention, a follow-back study of adult patients[41] indicates that among patients seen in adulthood with depression and anxiety, a number had previously been treated for anxiety symptoms in childhood, their disorder having persisted despite treatment. There is no information from these studies on whether neurological features distinguish those persons in whom the psychiatric disorder has been responsive to treatment from those in whom it has been resistant.

Organicity and Anxiety

Loretta Bender,[42] in her monograph *Psychopathology of Children with Organic Brain Disorders*, gave a good deal of prominence to the relationship between anxiety and organicity. She quoted Schilder's 1930 report, which said "Psychoanalysis of cases of anxiety neurosis had led us to the conviction that maturation behaviors in early childhood often have a fundamental influence on the further development of a neurosis," and then suggested that "any severe anxiety in a child that cannot be readily accounted for and corrected by a reality situation is invariably pointing to a threatening or disorganizing illness."

These comments were made on the basis of clinical experience and intuition and without the benefit of systematic research.

The mechanism linking neuromotor difficulties and anx-

iety suggested by Schilder[43] was that developmental delay, and with it a disturbance of equilibrium, creates a need for maternal help and support and that this need in turn encourages libidinous attachment to the parent and engenders neurotic conflict. Bender did not invoke libidinal theory but suggested that deep attachments form between the developmentally delayed child and its mother that lead to anxiety and stress when separation is threatened or initiated. The relationship would thus be an indirect one, with poor motor performance in early childhood eliciting strengthening attachment behaviors and dependency that persist through childhood and into adolescence.

We have no direct data to support or refute this suggestion, and there is no suggestion that the gross motor performance of children with soft signs is noticeably deficient. We failed to find an excess of parental psychopathologic abnormalities in sign-bearing anxious children, but a parent's promotion of anxious dependency in their child would not necessarily be accompanied by parental psychopathologic conditions.

The alternative, perhaps more parsimonious explanation is that some organic factor leads directly to anxious behavior. The likelihood of this explanation cannot be examined in the data obtained in the present study.

Soft Signs and Attention Deficit and Antisocial Disorder

We have found no relationship between these disorders and neuromotor performance. There were few cases of attention deficit disorder, although we similarly found no relationship in the study of a larger but overlapping sample of children studied at age 7.[1] These findings are in accord with those of Nichols and Chen,[21] who analyzed a large sample drawn from all 7-year-old participants in the National Collaborative Perinatal Project and found only a small excess of overactivity and inattention among children who had neurological soft signs. The remaining literature on soft signs and ADD is contradictory. Wikler et al[5] and Camp et al[18] found no difference in the prevalence of signs between children with and without ADD, although subjects in the latter study included children who were being treated with methylphenidate hydrochloride, which has been found to diminish deviant performance during the neurological examination.[44] Conversely, Mikkelsen et al,[45] Lucas et al,[16] and McMahon and Greenberg[17] all found signs to be more common in generally younger groups of children with ADD than in controls. Differences in behavioral and neurological criteria, small sample sizes, and diverse sample origins probably account for these contradictory findings.

A sizable number of children in our study sample were found to have severe conduct disorders. It had been our expectation that we would find an excess of these disorders in the children with soft signs, but we did not. The literature on the relationship between neurological dysfunction and antisocial behavior is conflicting. Studies such as our own and that by Rutter and associates,[46] carried out on clinically unselected samples, have failed to find any relationship, whereas case-control studies, such as that by Wolff et al[47] and Lewis et al,[15] have done so. Given that the determinants of soft signs remain largely unknown and that the service referral pathways for delinquents are exceedingly complex, such findings are difficult to interpret.

Origins of Soft Signs

The origins of soft signs remain obscure. It is widely held that they have a developmental origin,[48,49] by which is usually meant that they diminish in prevalence or severity with age. This hypothesis is supported to some extent by cross-sectional studies that find a higher prevalence of individual signs among younger than older children.[4,18,45] However, there have been relatively few longitudinal studies other than our own, and we found that a large proportion of children who had soft signs at age 7 continue to show such signs at age 17 (Shafer et al, unpublished data, 1984; and SN-C Ng, S. Q. Shafer, C. J. Stokman, et al, unpublished data, 1984). Hertzig,[50] who studied a neurologically deviant population, found that although there is a diminution in the amplitude and range of signs found in an individual child, children with a sign at one age are likely to show signs, not necessarily the same ones, five years later. Further, the notion of signs being "developmental" is not in itself contributory. The present report does not address the issue of the antecedents of soft signs. We have reported elsewhere[1] that we found no differences in the records of all children with soft signs and with controls on a range of prenatal and perinatal variables. The study by Nichols and Chen[21] on the cohort of children from the entire National Collaborative Perinatal Project at age 7 found few prenatal predictors, other than maternal smoking or diabetes and chorionitis, to be related to soft signs. Although the relative risk for having soft signs given one of these maternal factors was significantly increased, it was nevertheless low. Postnatal infections, illnesses, and injuries did not predict soft signs.

Nichols and Chen[21] also studied concordance for signs among the monozygotic and dizygotic twins in the study population. The difference between them was statistically significant, with greater concordance being found in the monozygotic twins. This finding coupled with observations on the ratio of concordance between full siblings and first cousins is compatible with a genetic origin of soft signs.

CONCLUSIONS

We have demonstrated a relationship between neurological abnormalities at age 7 and subsequent affective and anxiety disorders at age 17. There was evidence that anxiety diagnosis at age 17 was related to anxious dependent behavior in early childhood. The design of the study allowed for checks on consistency of findings, and the observed association was found in samples drawn from the different sexes and from the same children at different ages. The consistency of the findings coupled with an apparent dose-response relationship and our ability to comply with other methodological criteria support their validity. We have attempted to disprove the findings by searching for confounding relationships with IQ, social and environmental factors, and artifacts of test performance but have been unable to do so.

These findings have implications for our understanding of the nature and natural history of anxiety disorders in childhood and adolescence and for the prevention of persistent disorder throughout childhood and into adolescence.

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