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Infantile Autism: A Total Population Study of Reduced Optimality in the Pre-, Peri-, and Neonatal Period[1]

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Twenty-five autistic children, constituting a total population sample of children with infantile autism, were compared with 25 sex- and maternity-clinic-matched controls for occurrence of reduced optimality in the pre-, peri-, and neonatal period, as noted in medical records. Autistic children showed greatly increased scores for reduced optimality, especially with regard to prenatal factors. The findings are at odds with early reports that children with autism had not suffered potential brain injury. The reasons for the discrepancy are discussed.

INTRODUCTION

Well-controlled studies have failed to provide evidence for the hypothesis that there exists a causal relationship between infantile autism and abnormalities of parent-child interaction (for overview see Rutter & Schopler, 1978; Wing, 1980). To the contrary, evidence is accumulating that suggests basic brain dysfunction in infantile autism (Rutter & Lockyer, 1967; Small, 1975; Folstein & Rutter, 1977; Student & Sohmer, 1978; Gillberg, Trygstad, & Foss, 1982). Several studies on the obstetrical histories of autistic children have been published (e.g., Lobascher,

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Kingerlee, & Gubbay, 1970; Kolvin, Ounsted, & Roth, 1971; Knobloch & Pasamanick, 1975; Finegan & Quarrington, 1979; Deykin & MacMahon, 1980), and most of them point toward an increase of pre- and perinatal hazards.

The present paper reports on reduced optimality in the pre-, peri-, and neonatal period in a Swedish total population sample of autistic children. The uniform organization and data recording of Swedish obstetrical and neonatal departments is a unique advantage in studies of this kind. Also, the optimality/reduced optimality concept is applied here for the first time in the study of infantile autism.

METHOD

Subjects

All pediatricians and child psychiatrists working in a circumscribed geographical area (the region of Göteborg) were contacted by letter and asked if they knew of any child with "infantile autism, childhood schizophrenia, childhood psychosis, mental retardation with autistic traits, severe disturbance of social relationships plus speech-language disorder or severe compulsive disorder." One of the authors of the present article (C.G.) works as child psychiatric consultant to the institutions for psychotic children in Göteborg and had personal knowledge of more than half of the cases eventually reported by doctors, psychologists, and, as it turned out, nurses and teachers. All cases reported were examined by this author. Infantile autism was diagnosed in cases with early onset (before 2½ years of age) disturbance of ability to relate to people in combination with severe speech-language disorder and behavior problems (stereotyped mannerisms, severe ritualistic traits, or insistence on sameness) (Rutter, 1978). For details of the epidemiological survey, the reader is referred to Gillberg (1983). It merits mention that all autistic children of the study who were 7 years or older at the time of the screening had previously been diagnosed as "infantile autistic" or "psychotic" by at least one other, independent, child psychiatrist.

Twenty-six children born in the years 1962 through 1976 and living in the region of Göteborg by the end of 1980 fulfilled the criteria for infantile autism. This represents a prevalence figure of 2.0 per 10,000. As is argued elsewhere, the prevalence figure is likely to be fairly accurate, although a few autistic children with severe mental retardation and possibly even fewer autistic children of average or above-average intelligence might have been missed (Gillberg, 1983). Social class for the autistic children was no

different from that in the general population (Gillberg & Schaumann, 1982). One boy was excluded as he was born abroad and pertinent data about his pre/peri/neonatal period were not available. The boy:girl ratio in the remaining group of 25 children was 3.2:1. Twenty percent of the children were in the normal or near-normal IQ range according to psychological testing, while the remainder had tested IQs of < 70 or were considered untestable. Sixteen percent of the children have hitherto developed epilepsia. One girl (who also suffers from epilepsia) and one boy are affected by neurofibromatosis. For each autistic child a same-sexed control born in the same obstetric department was chosen. Time of birth had to be as chose as possible to that of the autistic child.

Procedure

Swedish obstetric and neonatal care is uniformly organized, and data recording is done in accordance with highly structured manuals. All obstetric and medical records of relevance for the present study were collected and analyzed for the 25 autistic and 25 control children. All records were analyzed blindly, e.g., without knowledge of whether the child belonged to the index or the control group.

The concept of reduced optimality with regard to pregnancy and intrapartal factors was introduced by Prechtl (1968), who later showed it (1980) to possess the capacity for self-weighting by accumulation of non-optimal points and for detecting intercorrelations between nonoptimal factors in the study of newborn neurological abnormalities. Touwen and co-workers (Touwen, Huishes, Jurgens-v.d.Zee, Bierman-van Eendenburgh, Smrkovsky, & Olinga, 1980) pointed to its usefulness as a prognostic instrument in the follow-up of neurological morbidity in the newborn period.

The optimality/reduced optimality scoring of pre/perinatal factors was not originally developed for use in the study of background factors in neurological/neurodevelopmental conditions, but rather to identify high-risk pregnancies for intensive antenatal surveillance. Recently, however, the Michaelis group (Michaelis, Haug, Majewski, Bierich, & Dopfer, 1980) in Germany demonstrated that it is indeed a good method to study background factors in the fetal alcohol syndrome and cerebral palsy. The Hagberg group (Kyllerman, Note 1; Kyllerman & Hagberg, Note 2) in Sweden confirmed its usefulness in the study of background factors in cerebral palsy. One of the authors of the present article used a modified version of the Prechtl list of optimal conditions to identify potentially neuropathogenic background factors in a study of perceptual, motor, and attentional deficits in Swedish 7-year-old children (Gillberg & Rasmussen, 1982). The same list was used in the present study (Table I) and bears

Table I. Pre-, Peri-, and Neonatal Conditions Studied

Pre-, peri-, and neonatal factors	Optimal
Prenatal factors	
Maternal age	20-30
Parity	1-2
Abortions in history	0-2
Bleedings in pregnancy	absent
Severe infections in pregnancy	absent
Generalized edema	absent
Albuminuria	absent
Blood pressure	< 140/95
Psychiatric specialist care	no
Maternal diabetes or epilepsia	absent
Medication	< 1 week[a]
Gestational age (weeks)	36-41
Smallness for gestational age	no[b]
Intrapartal factors	
Twins or multiple birth	no
Breech, foot, or other abnormal presentation	no
Vacuum extraction	no
Epidural anesthesia	no
Apgar score	9-10
Cord prolapse/around neck/knot	no
Amniotic fluid	clear
Child severely traumatized (fractures, lots of petechiae)	no
Neonatal factors	
Respiratory distress	absent
Septicemia/meningitis	absent
Hyperbilirubinemia	absent[c]
Anemia requiring transfusion	absent
Irritable infant, floppy infant/ convulsions	no
Difficulties regulating temperature	no
Clinical dysmaturity	no[d]
Oxygen treatment > 30%	no

[a]Only medication with well-known or suspected negative effect on the fetus (barbiturates, sulphonamides, chlorotalidon, furosemide, and hydrochlorothiazide in the present study).
[b]Weight below the −2 *SD* limit for gestational age.
[c] > 15 mg % in children with birthweight ≤ 2,500 g; > 20 mg % in children with birthweight > 2,500 g.
[d]Scaling skin that appears to be too large for the body—included only if diagnosed by experienced pediatricians.

close resemblance to the Kyllerman-Hagberg list. It was developed to comply with the Swedish obstetric-neonatal recording system and the retrospective nature of the study. Some items, such as placental infarction, were not included, because they were shown to be over- or underreported depending on different routines in different obstetric departments. Transient hypoglycemia may be of such short duration as to pass clinically unnoticed and was therefore not included. Hypoglycemia was not diagnosed in any child in the present study.

For each factor with optimal conditions a score of 0 was given, and for each factor with conditions outside the optimal range a score of 1 was given. All scores for individual items were then added to obtain a total score for reduced optimality in the pre-, peri-, and neonatal period. The maximum total reduced score in this version is 29. In a sample of the total population without signs of perceptual, motor, and attentional deficits, the mean total reduced score was 2.6 ± 1.2 ($N = 51$).

Fisher's nonparametric permutation test (Bradley, 1968) was used in the statistical analysis of the results.

RESULTS

As can be seen in Table II, the autistic subjects had much higher total scores for reduced optimality than did controls. A total of 725 nonoptimal points was possible in each group (29×25). The sum total of nonoptimal points was 137 (18.9%) in the autism group and 53 (7.3%) in the control group ($p < .001$).

Forty-eight percent of the cases with infantile autism had total scores above the 95th percentile of the control group ($p < .001$) (Figure 1). Thirty-two percent of autistic children had prenatal scores above the 95th percentile of the control group ($p < .01$). The same was true of neonatal scores.

Boys and girls of the autism group showed equally high values (mean $\pm$ $SD = 5.5 \pm 2.8$, $N = 19$ and 5.8 ± 1.6, $N = 6$, n.s.).

Maternal age was significantly raised in the autistic sample (for further details, see Gillberg, 1980). Table III shows the association between maternal age and reduced optimality other than high or low maternal age. There was a tendency toward more reduced optimality with high maternal age, but this was true only in cases when the mother was 35 years of age or older at the time of birth of the child.

Signs of clinical dysmaturity, bleedings in pregnancy, and pre/post-maturity were the only other single factors that were signicantly ($p < .01$, .05, and .05, respectively) more common in the autistic than in the control group (Table II). However, other factors, such as severe infection in pregnancy, generalized edema, medication > 1 week, and

Table II. Distribution of Nonoptimal Factors in Individual Children

Autism group	Case number	Child's sex	Maternal age	Parity	Abortions	Bleedings in pregnancy	Infection in pregnancy	Generalized edema	Albuminuria	Raised blood pressure	Psychiatric treatment	Medication > 1 week	Gestational age	SGA	Twins/multiple birth	Abnormal presentation	Vacuum extraction	Apgar score reduced	Cord complications	Amniotic fluid not clear	Child traumatized	Respiratory distress	Septicemia/meningitis	Hyperbilirubinemia	Irritable/floppy infant	Clinical dysmaturity	Oxygen treatment > 30%	Total nonoptimal score
1	m		+	+		+		+	+		+	+	+				+	+		+	+				+			11
2	m		+			+		+	+	+		+	+ (+)											+				11
3	m				+	+		+			+		+					+										8
4	m		(+)[a]	+	+	+			+			+	+					+										8
5	m		(+)			+		+								+	+											8
6	f		+	+		+		+	+			+	(+)						+									8
7	m					+		+	+	+		+	+	+								+			+			7
8	m		+	+		+	+	+				+	+					+										7
9	f										+			+														7
10	m		+			+	+					+						+										6
11	f											+	(+)					+		+								6
12	f		+			+						+																6
13	m		+	+									+		+				+		+							5
14	m					+		+				+								+								5
15	m					+	+	+																				4
16	m						+	+																				4
17	m			+			+	+																				4
18	f			+		+							+															4
19	f			+		+							+							+								4
20	m								+				+															3
21	m		+	+																								3
22	m		+	+									+							+								3
23	m		+										+							+								3

[a] Twin.

24	m					+		+																					2
25	m	+																	+										2
	Sum	18		9	1	11	7	12	6	3	3	10	12	3		1	1	3	6	3	6	3		1	2	1	5	11	1	137
significant difference vs. control		.01				.05							.05															.01		.001
Control group																														
1	m	+				+		+					+			+	+	+										+		8
2	m	+		+				+	+										+		+									5
3	m							+		+					+					+										5
4	m	+		+		+						+				+														4
5	m							+	+	+										+										4
6	f	+					+					+							+											4
7	f			+			+	+				+																		4
8	m												+							+										2
9	m			+															+											2
10	m	+		+																											2
11	m			+						+																					2
12	f																		+	+										2
13	f														+												+			2
14	f							+				+																		2
15	m	+																													1
16	m			+																											1
17	m																							+						1
18	m												+																		1
19	m										+																				1
20	m																														0
21	m																														0
22	m																														0
23	m																														0
24	m																														0
25	f																														0
	Sum	6		7	0	2	2	6	2	3	1	4	3	0		2	2	1	1	4	4	0		1	0	0	1	1	0	53

[a]( ) = low maternal/gestational age.

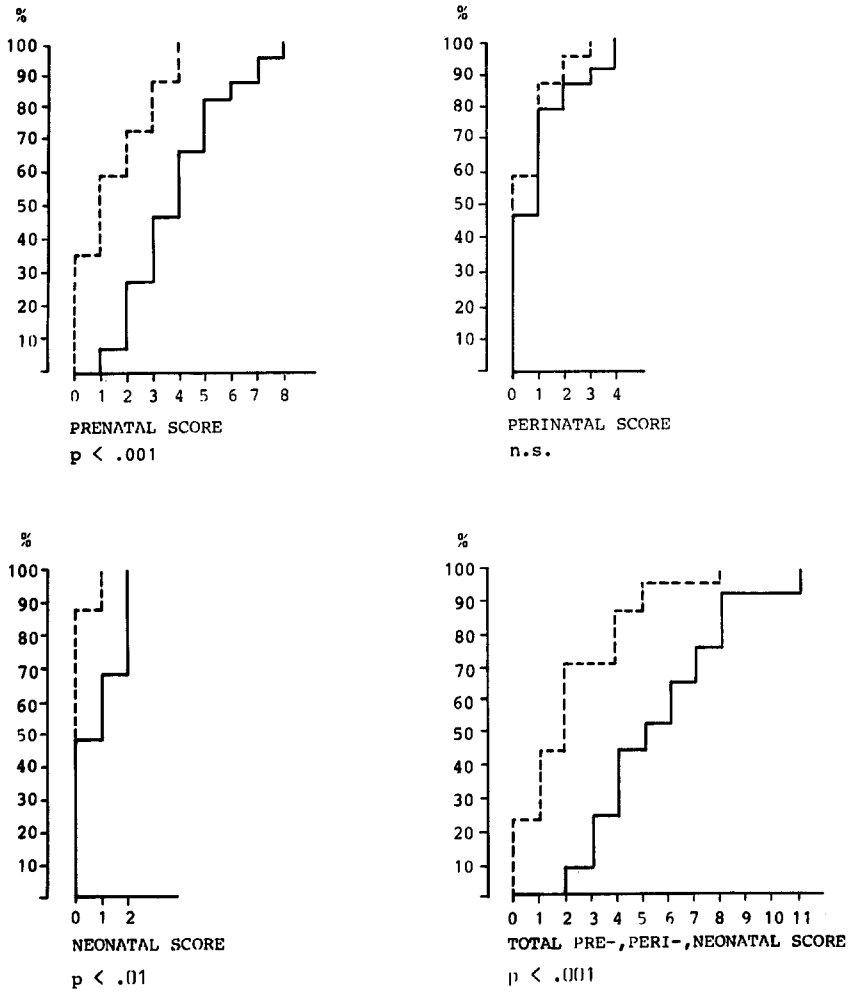

Fig. 1. Cumulative frequency distribution of reduced optimality scores in the pre-, peri-, and neonatal period in the autism (————) and control (----) group.

reduced Apgar score, were also more common in the autism group, although the differences fell short of statistical significance.

Birthweight did not differ significantly between the groups (mean ± *SD* = 3,480 ± 620 in the autism group and 3,647 ± 504 in the control group).

Edema occurred in young mothers as often as in older mothers, both in the autism and the control group. The same was true of albuminuria, high blood pressure, bleedings, infections, medication, reduced Apgar score, and clinical dysmaturity.

Table III. Reduced Optimality Score in the Pre-, Peri-, and Neonatal Period (Except Maternal Age) in Relation to Maternal Age at Birth of Child

Maternal age at birth of child	Mean reduced optimality score (± *SD*)
< 20	7 ± 0 (*N* = 2)
20-34	3.9 ± 2.1 (*N* = 16)
≥ 35	6.6 ± 2.6 (*N* = 7)

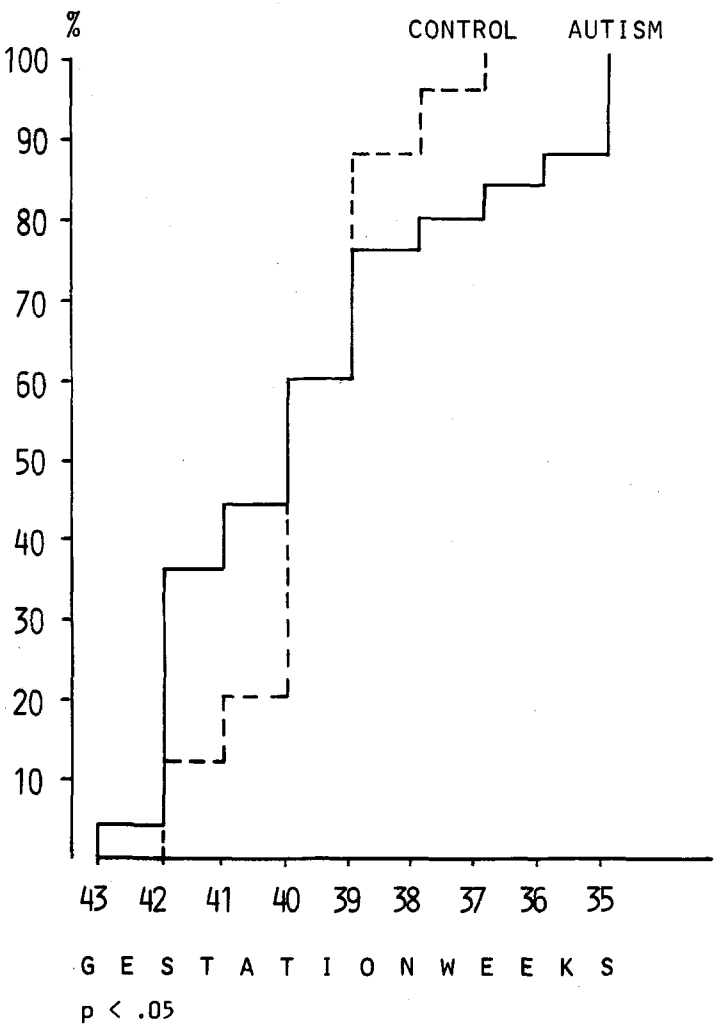

Fig. 2. Cumulative frequency distribution of number of gestational weeks in the autism (——) and control (------) group.

As one nonoptimal factor often ran parallel with other nonoptimal conditions, many of the nonoptimal factors studied showed some association with other, randomly chosen, nonoptimal factors.

All autistic children with a reduction of optimality in the peri- and/or neonatal period showed reduced optimality in the prenatal period too. A majority of the control group cases showed the same association between prenatal and peri/neonatal reduced optimality. Thus, unfavorable peri- and neonatal conditions tended not to be "separate" risks but rather to be "signals" in the child that pregnancy had been nonoptimal. This was particularly pronounced with regard to the group of autistic children who had shown clinical dysmaturity in the newborn period, where the mean prenatal total score ± *SD* was 4.4 ± 1.9 ($N = 11$) compared with 3.3 ± 1.8 ($N = 14$) in the autistic group without clinical dysmaturity ($p < .05$).

Seven of the 12 mothers with generalized edema in the autism group had been treated with furosemide or chlorothiazide. Two of these had also been treated with sulphonamides in pregnancy. In the control group only 1 of the 6 mothers with generalized edema had been treated with diuretics.

Seven of 12 mothers (58%) with edema had autistic babies who were clinically dysmature. Four of the 13 mothers (31%) without edema in this group had babies who were dysmature.

The distribution of gestational age (Figure 2) was much more homogeneous in the control than in the autism group.

All the cases of irritable/floppy infant/convulsions were accounted for by irritable and floppy babies. Convulsions did not occur in any child of the present material.

Autistic children with IQ > 70 ($N = 5$) had total scores as high as those with lower IQs (mean ± *SD* = 6.0 ± 3.4 versus 5.5 ± 2.4, n.s.).

None of the autistic children in the present study came from the highest social class (class I). The total score in children from social class II was almost exactly the same as that in children from the lowest social class (class III) (mean ± *SD* = 5.6 ± 3.3 versus 5.5 ± 2.0, n.s.).

DISCUSSION

One might argue that the list of optimal conditions used in the present study is of little avail as the weighting capacity inherent in the 0-1 scoring leads to important factors being missed and unimportant factors being overemphasized. Much as this criticism is fair, it does not take account of the fact that if only factors with known neuropathogenic effect were analyzed, no development as regards the understanding of hitherto unknown pre-, peri-, and neonatal adverse mechanisms would be possible.

Furthermore, at the present time, there is no generally accepted weighting system even for factors with well-established neuropathogenic risks. Also, in studying only single factors, one misses what is perhaps the main point, namely, that neurohandicaps in the child are possibly more often due to the additive effect of repeated adverse events in pregnancy and the newborn period than the result of one single insult to the brain.

The very high scores for reduced optimality in the pre-, peri-, and neonatal period found in the autistic sample of this study (48% of autism cases showing total reduced scores above the 95th percentile of the control group) agrees well with recent research in this field (e.g., Harper & Williams, 1974; Finegan & Quarrington, 1979) but is somewhat at odds with earlier studies. The main reason for this is possibly discrepancies in reliability of data sources rather than in diagnostic criteria. The present study is unique in that it refers to uniformly recorded background data for autistic children as well as for maternity-clinic matched controls.

Some of the earlier studies on perinatal conditions in autism (e.g., Finegan & Quarrington) have been cautious in drawing firm conclusions since the overrepresentation of boys in the autism group was not matched by a corresponding overrepresentation in the control groups. Boys are more frequently affected by most perinatal hazards than girls (Broman, Nichols, & Kennedy, 1975). Because of the sex match of the present study, the possibility that such an association might account for the results could be ruled out.

The Finegan-Quarrington study used siblings of autistic children as one comparison group. A detailed survey (including hereditary, perinatal, and psychosocial factors) of the siblings of autistic children in this study is currently in progress. Preliminary data point in the same direction as the results of the Canadian study, i.e., that unaffected siblings of autistic children have much less reduced optimality scores.

The rate of reduced optimality in the prenatal period was much more increased in the autism group than were the rates of intrapartal or neonatal reduced optimality. Generalized edema, pre- or postmaturity, medication, and uterine bleeding in pregnancy were the single adverse factors most often encountered apart from high maternal age. Clinical dysmaturity appeared as a neonatal complication much more often in the autism group than in the control group. These results are in accordance with later studies (e.g., Torrey, Hersh, & McCabe, 1975; Finegan & Quarrington, 1979), whereas earlier research has stressed the importance of intrapartal complications (e.g., Lobascher et al., 1970).

Our data do not suggest a unifying pathological process, and the single factors discriminating between the autism and control groups are not those carrying the strongest likelihood of brain damage. The same tendency was found and commented on in a recent study by Deykin and

MacMahon (1980). This contrasts with the findings obtained in, e.g., cerebral palsy, where such factors as preterm birth and asphyxia (factors known to carry a high risk of brain damage) are of major importance.

Scores for prenatal reduced optimality were particularly high in the group of children showing signs of dysmaturity in the neonatal period. This is consistent with the notion that dysmaturity is an extrauterine sign of relative intrauterine undernutrition. Thus, it appears that the high rate of dysmaturity in the autism group is merely a reflection of the reduced optimality in the prenatal period and not in itself a neuropathogenic factor.

It is of some interest to compare the results of the present study with those obtained by one of the authors in a study of so-called MBD (minimal brain dysfunction) syndromes (motor-perceptual problems in combination with signs of attention deficit) in which exactly the same scoring system was used (Gillberg & Rasmussen, 1982). MBD cases of that study showed a mean score for reduced optimality in the pre-, peri-, and neonatal period of 4.1 ± 1.2 (N = 42). This figure should be compared with that of 5.6 ± 2.5 (N = 25) found in the autism cases of the present study.

In a recent investigation of reduced optimality in cerebral palsy, Kyllerman (Note 1) found a total nonoptimal rate of 23% in dyskinetic cerebral palsy using a scoring system similar to the one used in the present study (34 aspects were analyzed in the Kyllerman study compared with 29 in the present one). The corresponding figure in the autism group reported here was 19%. The figures in the control groups were 6% and 7%, respectively, in the two studies. The findings reveal that children with infantile autism are more heavily affected by reduced optimality in the pre-, peri-, and neonatal period than children diagnosed as suffering from MBD, but not quite so heavily affected as those suffering from dyskinetic cerebral palsy.

High maternal age increases the risk that the child may suffer from infantile autism (Gillberg, 1980). The high rate of pre-, peri-, and neonatal complications associated with maternal age ≥ 35 years is possibly one reason for this increased risk.

Low or high social class was not associated with the occurrence of reduced optimality. This is important to emphasize as someone might argue that in early reports on autism (e.g., the original article by Kanner, 1943) only upper class cases were included and in such cases there were allegedly optimal pre-, peri-, and neonatal conditions. It is possible that these early findings are a reflection of variability in data sources rather than an effect of the high social class.

It is unlikely that the association seen between infantile autism and reduced optimality would be merely an association with the concomitant

mental retardation. Autistic children with relatively higher IQ levels were just as heavily affected by reduced optimality as were those with very low IQ.

In a twin study, Folstein and Rutter (1977) have shown that hereditary factors play an essential part in the genesis of infantile autism. Their study also demonstrated the overrepresentation of perinatal complications in autism cases discordant for autism. Thus, potentially neuropathogenic factors may be of major importance too. The present study provides further support for this. Some caution is, however, warranted in the interpretation of the reduced optimality scores in autistic subjects. It is possible that some of the reduced optimality is not a reflection of adverse factors causing damage to the child's brain but rather of some primary defect (genetic?) in the fetus manifesting in various pre- and perinatal "events." In future studies it will be necessary to consider both of these aspects. Hereditary and neuropathogenic factors possibly in some cases act together in the shaping of a biological disorder starting in fetal life or early infancy and causing immense distress and sorrow in parents and siblings.

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