In Search of Prediction Factors for Autism Spectrum Disorders: An Impossible Task?

Rene Pry¹, Arne F. Petersen², Amaria Baghdadli³
¹Université Paul Valéry & CHU-Montpellier, Montpellier, France
²Centre de Ressource Autism, CHU-Montpellier, Montpellier, France
³Child & Adolescent Psychiatry, CHU-Montpellier, Montpellier, France
Email: rene.pry@univ-montp3.fr

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Clinical work and prediction of development are closely linked in the practice of early detection, diagnosis and choice of modes of intervention in young children with autism. Variables are often defined in terms of risk factors or of development, and may refer to general or specific phenomena. The purpose of this paper was, using a generalized mixed model, to test ways of measuring development and its prediction regarding joint attention (that is to say, response to and initiation of joint attention) in children with autism. Over a period of one year, seventy-seven children were followed from the age of four and a half years upwards. The results show that it is possible to identify general risk factors, but much more difficult to pinpoint specific factors. In our current state of knowledge, prediction can only be of a global nature and therefore requires the use of general markers.

Keywords: Autism, Joint Attention, Prediction, GLMM, Risk Factor, General Marker

Introduction

A major part of the research and clinical work on children with pervasive developmental disorders is devoted to the question of prediction. Prediction is already implied in the early detection of the syndrome, but it becomes a special developmental problem once the diagnosis has been established, and it is finally evoked when treatment strategies are chosen. So far experience has shown that within these three domains the prognosis is not only uncertain but virtually impossible.

Possible Prediction Factors—An Overview

Prediction factors are usually considered in two perspectives: 1) from a developmental (temporal) viewpoint, opposing risk factors and developmental factors; and 2) from a clinical viewpoint which distinguishes global factors and specific factors.

1) Developmental perspective. Risk factors may be subdivided into primary, secondary, tertiary etc. factors—a classification which divides the pre-diagnostic period (for autism the first 30 months) into periods during which new competences known as normal development are expected to occur. Developmental factors are generally evolved from the time of diagnosis, which is also the starting point for most longitudinal studies.

2) Clinical perspective. Global or general markers for autism relate to the diagnosis, which is itself an outcome of composite evaluations like the ADI (Lord, Rutter, & Le Couteur, 1994, 2010), ADOS (Lord, Risi, Lambrecht, Cook, Leventhal, DiLavore, Pickles, & Rutter, 2000, 2010), or refer to the severity of the disturbance, which is also a result of composite assessments (CARS: Schopler, Reichler, DeVellis, & Daly, 1980), and other indices of gravity, IQ, as well as general markers for socio-adaptability like those in Daily Living Skills (DLS) of the Vineland Scale (Sparrow, Balla, & Cicchetti, 1984). These global scores possess emergent qualities which transcend the sub-scores they consist of (thus the whole does not equal the sum of its parts). Being real synthetic scores they express a clinical reality, that of the autistic syndrome. Specific or elementary markers, which refer to certain competences (such as synchronous imitation, joint attention, identification of facial expressions, prosodic modulation, vocabulary, etc.), are unfortunately more often than not coded in terms of “present/absent”, or marked “positive/negative”, even though their development may start discretely as precursor indices for global markers (Nadel, 2009).

Here it is noteworthy that, if we attribute a certain predictive value to these different factors, naturally we also have to subscribe to them a certain stability over time, or consider them as stable characteristics for individuals with autism.

By crossing the two main classifications we obtain a combination of prediction factors from which it is possible to articulate the developmental and clinical perspectives (Table 1).

But before addressing this question it is appropriate to note that various constraints complicate the very identification of the different factors. Among these constraints we shall consider the following: definition of the disorder (a complex and multifaceted phenomenon), its changing prevalence, the question of time-independence of the prediction factors, and the choice of statistical methodology.

A Global Definition

For the whole group of pervasive developmental deficits (PDD) the World Health Organisation’s ICD-10 classification (1994) is the most recommended. PDD includes various clinical
phenomena, which may be divided into seven categories (infan-
tile autism, atypical, Rett, disintegrative, hyperkinetic with
mental retardation, Asperger and others) or in a dimensional
respect (the notion of Autism Spectrum Disorders: ASD).
These two approaches cover the same clinical reality: they
identify qualitative and simultaneous impairments, reciprocal
social interactions, modalities of communication, as well as a
repertoire of interests and limited stereotyped, repetitive activi-
ties. This combination, which finds the notion of “disorder”,
cannot be merely fortuitous. As a consequence, this very asso-
ciation translates itself in reality by a multitude of formulations,
in terms of intensity or predominance of one impairment over
another, or again by a more or less discrete presence of diag-
nostic criteria (age, …).

It is evident that this phenomenon, being multifarious indeed,
may easily be the phenotypic expression of the same disorder
with different severity or signal several independent deficits.
Besides the ICD, which is an ongoing classification, foresees
with different severity or signal several independent deficits.
In terms of intensity or predominance of one impairment over
another, or again by a more or less discrete presence of diag-
nostic criteria (age, …).

Weak Prevalence and Prediction Factors That
Change with Time

For a long time pervasive developmental disorders were con-
idered for a long time considered to be a statistically rare phe-
omenon (4 in 10,000). Today, however, the prevalence is 6 to
7 for 1000 individuals under 20 years of age, and for autism 2
to 4 for 1000 individuals (Chaman, 2002; Fombonne, 2009).
The accuracy of identifying of risk factors depends on the
prevalence in so far as a weak prevalence produces a large
number of “false positives”. This phenomenon can be illus-
trated by some working data which we now have at our dis-
posal in a precocity survey for which there is high specificity
(= 98), but low sensitivity and a large number of “false posi-
tives” (= 38) as in the “Check-List for Autism in Toddlers”
(Baron-Cohen, Wheelwright, Cox, Baird, Chaman, Swetten-
ham, Drew, & Doelhing, 2001) and in the “Modified Check-
List for Autism in Toddlers” (Robins, Fein, Barton, & Green,
2001; Baghdadli, 2005).

While, in some cases, predicting a given illness or disorder
may not be too difficult, since the risk factors have been easily
identified (linked, say, to genes, neurological problems, radiation
exposure), it is quite another matter with pervasive develop-
mental disorders for which many factors will be in interaction
and probably of a genetic, neurological or environmental na-
ture.

Since the ways in which the risk factors are expressed change
with the child’s development and only become somewhat stabil-
lized when the child approaches 36 months of age, it seems
only possible to pronounce a reasonable diagnosis at this time
of maturation. By this we mean that the general markers, which
are present from early on, undergo differentiation and seem-
ingly end up “coinciding” with the characteristics of the disor-
der. For practical reasons it may be helpful to break down and
analyse the risk factors in view of a temporal organisation for
normal development during the sensorimotor period: 1) The
neonatal and perinatal phase; 2) The 2-month-old phase (with
social smile, intentionality and interplay with a partner); 3) A
phase at nine months (when triadic competences and joint at-
tention appear); and 4) A phase at eighteen months (when the
symbol function emerges) (Rochat, 2001). For each of these
phases the particularities of children with PDD may then be
noted, such as missing or non-developed abilities, regression or
temporary disappearance of skills, etc.

The only risk factors for PDD bearing upon the neo-
and perinatal phase, which have been identified so far, are those
of sex-ratio (four times more common in boys than in girls),
the age of the parents (the risk is multiplied by 1.3 for mothers
over 35 years of age and by 1.4 for fathers aged over 40), the
presence of another affected child among the siblings (45% higher
risk if the affected child is a boy, 17% higher risk if it is a
girl). The risk strongly increases (25% to 30%) if the family al-
ready includes two children with PDD, and the syndrome concor-
dence between monozygote twin boys varies from 70% to
90%. Finally, it seems that incidences of pre- and perinatal
antecedents are more common in individuals with PDD than in
the population as a whole.

Retrospective studies, especially those that include analyses
of family films, have also revealed unusual behavioural traits,
first and foremost in spontaneous motricity (Rogers & Beneto,
2002; Fournier, Hass, Naik, Lodha, & Cauraugh, 2010), but
also in variations of tones and peculiarities in sensory and at-
tention processing. However, these markers remain very gen-
eral and not functionally specific, even though they may derive
from a particular sensorimotor functioning, and at present we
do not dispose of enough relevant statistical data on prevalence,
sensitivity and specificity. Results of longitudinal studies, from
the age of 12 months, on brothers and sisters, born after a sib-
lings with autism, attach a tentative predictive value to the ab-
sence or rareness of social smile, eye contact, and orientation

Table 1.
Factors and variables used in prediction studies.

<table>
<thead>
<tr>
<th>Explanatory variables</th>
<th>Factor</th>
<th>Elementary</th>
<th>Global</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk</td>
<td>Social smile</td>
<td>Genetic load</td>
<td></td>
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<tr>
<td></td>
<td>Reaction to call-name</td>
<td>Neonatal history</td>
<td></td>
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<td></td>
<td>Joint attention</td>
<td>Sensory orientation</td>
<td></td>
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<td></td>
<td>Fantasy play</td>
<td>Tonico-postural regulation</td>
<td></td>
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<tr>
<td></td>
<td>Productive lexicon</td>
<td>Spontaneous motor activity</td>
<td></td>
</tr>
<tr>
<td>Developmental</td>
<td>Special treatment program</td>
<td>Diagnostic markers</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Delay/specific hyper competence</td>
<td>Associated disorders</td>
<td></td>
</tr>
<tr>
<td>Variables to be explained</td>
<td>Linguistic activity</td>
<td>Intensity of the treatment</td>
<td></td>
</tr>
<tr>
<td>Prediction</td>
<td>Interactive competences</td>
<td>Intellectual level</td>
<td></td>
</tr>
<tr>
<td>Behavioral disorders</td>
<td></td>
<td>Clinical development</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Psycho-social development</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Everyday autonomy</td>
<td></td>
</tr>
</tbody>
</table>

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Stability and Instability of Developmental Factors

Even though the number of interacting factors of development is considerable, it has nevertheless been possible to classify variables such as the conditions of appearance and precociouslyness of the disorders, their importance in terms of symptom intensity, the presence of associated troubles (intellectual deficiency, epilepsy, somatic pathologies), and environmental factors. Among the latter, certain modalities of care and support seem to be of importance, although, even today, it is difficult to evaluate the exact impact of treatment on development; this being said, some results lead us to think that precocity, intensity of the proposed stimulation, and structural adaptation of the environment may be of positive influence (Montreuil & Mageotte, 1994; Recordon-Gabonaud, 2009).

In fact, the factors that best account for socio-cognitive development in autism are general markers derived from developmental quotients, e.g., IQ, established by evaluations on different levels of development regarding adaptive functions assessed at the time of diagnosis. These general markers are composite and come from very heterogeneous developmental domains (motor, cognitive, social, linguistic, etc.). In every second child with autism, the scores of the intelligence test increase significantly with age (Fry, Juhel, Bodet, & Baghdadi, 2007). Moreover, between childhood and adulthood a tendency towards a decrease in the “non-verbal” component can be observed in tempo with a moderate increase in the “verbal” component (Seltzer, Shattuck, Abbeduto, & Greenberg, 2004; Mashhood, Howlin, & Rutter, 2000). It should also be noted that in children with “IQ-extremes” like <50 and >100 one observes a more disadvantageous prediction than in the population with IQ’s < 100 and >50. Likewise, the presence of language at the time of diagnosis is important: the variable to be explained must be quantifiable, the residuals must follow a normal law and be independent, the explicative variables must not be redundant, and the robustness of the model must be tested (ruining the extreme cases). In practice, and more precisely in developmental psychopathology, these conditions are rarely united, and we often see situations of multi-linearity between prediction factors.

In logistic regression the variables may be qualitative (in general binary), multi-nominal (when there are more than two classes), or enumerative (e.g., number of hours of treatment) as in the Poisson regression model. These models are sufficiently adapted to the complex problem of prediction for linking up a diagnosis or a development (binary variable) with a group of risk factors with which one tries to characterize the respective weight. The strength of such links may be expressed in terms of excess risk, relative risk, “odds ratio”, or attributable risk.

The characteristics of “regression diagnosis” are the independence of residues, the detection of “likely” subjects, at the origin of important variations (robustness of the model) and the search for multi-linearity.

Generalized linear models mixed with repeated measures are techniques with a theory of high content and much in use: these techniques are applied in areas as diverse as forestry, medicine, finance, economy, industry and so forth. They are most interesting since they can be used to analyze diverse effects and repeated measurements, and they are ready for use with different probability laws with a view to modeling errors, and even more so as their distributions belong to the exponential family (which is often found in developmental psychology).

On the basis of all these remarks one may ask how the interactions between the different classes of variables take place over a given period (does a predictive variable at a given time explain the same percentage of variance later on)—i.e. the developmental perspective—and to question whether the data collected at the moment of the diagnosis are informative with respect to a specific competence—i.e. the clinical perspective.

Methodology: Population Characteristics, Developmental Factors and Target Variables

The present study was coordinated by the Languedoc-Roussillon Autism Resource Centre at the CHU in Montpellier. Seventy-seven children with autism were examined three times at intervals of 6 months: T1, T2 (T1 + 6 months) and T3 (T1 + 12 months).

The diagnoses were worked out on the basis of multidisciplinary, clinical observations guided by the standardized version of international classifications of mental and behavioral disorders (ICD-10, WHO, 1994) and by using the “Revised Autism Diagnostic Interview” (Lord, Rutter, & Le Couteur, 1994), ADOS (Lord, Risi, Lambrecht, Cook, Leventhal, DiLavore, Pickles, & Rutter, 2000) and the “Childhood Autism Rating Scale” (Schopler, Reichler, DeVellis, & Daly, 1983). Children with pronounced motor delay on levels of less than 18 months were not included, as the aspects of rehabilitation, by increasing the prediction, may hide the variability of the rest of the sample.
A descriptive analysis of the population of 77 children was carried out by calculating the frequency of the quantitative variables, the median and the interquartiles (75% and 25%) for the qualitative variables (their distribution not always being Gaussian, the normality of the distributions was analysed with the help of the Shapiro-Wilks Test).

The sample presented two diagnostic categories: 87% (67) of the children suffered from infantile autism and 13% (10) from atypical autism. It included 66 boys (86%) and only 11 girls (14%): thus the sex-ratio is 6/1 which was slightly above the ratio found in epidemiological studies, whose only inclusion criterion is the diagnosis of autism or that of other PDDs. In return this result is in agreement with those obtained in populations with autism without mental retardation. The median age at the beginning of the observation period was 52 months with an interval included between 35 months for the youngest child and 60 months for the oldest child and an interquartile 25/75 between 48 and 59 months. The level of expressive language was assessed with item 19 of the ADI-R: (0 = production of phrases; 1 = fewer than 50 words; 2 = fewer than 5 words). The two main forms of motor development (global and fine) were explored with the two revised Brunet-Lézine subscales: oculo-manual coordination and postural development. Regarding motor development, the median level of oculo-manual coordination was 20 months with an interquartile included between 18 and 24.5 months, and the median postural level was evaluated as being around 24 months with an interquartile included between 20 and 30 months. These data are presented in Table 2.

The levels of socio-adaptive development were assessed by the Vineland Scale or VABS (Sparrow, Balla, & Cicchetti, 1984). This scale evaluates the children's adaptation level in the functional domains of communication, socialisation, autonomy in everyday life, and motor development. The American norms of the Vineland Adaptive Behaviour Scale also apply to the French population (Fombonne & Achard, 1993; Pry, Guillain, & Foxonet, 1996), and there is a specific standardisation for sub-populations with autism (Carter, Volkmar, Sparrow, Wang, Lord, & Dawson, 1998; Freeman, Delhomme, Guthue, & Zhang, 1999).

The variable to be explained was joint attention, which was assessed by using the ECSP-Scale (Guidetti & Tourette, 1993), adapted to the Early Social Communication Scale (Seibert & Hogan, 1982). This last scale evaluates the development of skills for establishing shared attention to the same object, person, event or topic. Two kinds of reactions were studied: 1) Response to joint attention. The aim here was to describe the Table 2.

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Typical</td>
<td>67</td>
<td>87</td>
</tr>
<tr>
<td>Atypical</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>Age (months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>25% - 75% percentile</td>
<td>48</td>
<td>59</td>
</tr>
<tr>
<td>Age at detection* (months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>25% - 75% percentile</td>
<td>8.75</td>
<td>24</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>66</td>
<td>85.7</td>
</tr>
<tr>
<td>Female</td>
<td>11</td>
<td>14.3</td>
</tr>
<tr>
<td>SPC**</td>
<td></td>
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<tr>
<td>Low</td>
<td></td>
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<tr>
<td>Average</td>
<td>23</td>
<td>29.9</td>
</tr>
<tr>
<td>High</td>
<td>41</td>
<td>53.2</td>
</tr>
<tr>
<td>Median</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>25% - 75% percentile</td>
<td>18</td>
<td>31</td>
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<tr>
<td>CARS</td>
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</tr>
<tr>
<td>Median</td>
<td>33</td>
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<tr>
<td>25% - 75% percentile</td>
<td>26.5</td>
<td>36.5</td>
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<tr>
<td>ADI-R</td>
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<td></td>
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<tr>
<td>Social interactions (&gt;5)**</td>
<td>69</td>
<td>93</td>
</tr>
<tr>
<td>Few interests (&lt;5)</td>
<td>65</td>
<td>88</td>
</tr>
<tr>
<td>Anomalies before 36 months (&gt;1)</td>
<td>74</td>
<td>100</td>
</tr>
<tr>
<td>ADOS-G</td>
<td></td>
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<tr>
<td>Module 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social interactions: m (sd)</td>
<td>15.08 (4.8)</td>
<td>74</td>
</tr>
<tr>
<td>Repeated behaviour</td>
<td>3.67 (1.35)</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Module 2</td>
<td></td>
<td></td>
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<tr>
<td>Social interactions: m (sd)</td>
<td>13.92 (4.1)</td>
<td>26</td>
</tr>
<tr>
<td>Repeated behaviour</td>
<td>2.67 (1.4)</td>
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</tr>
<tr>
<td>N</td>
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<td></td>
</tr>
<tr>
<td>Expressive language: Item 19 ADI</td>
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<tr>
<td>Good: Phrases: N (%)</td>
<td>20</td>
<td>26</td>
</tr>
<tr>
<td>Middle: &gt;5 words</td>
<td>30</td>
<td>26</td>
</tr>
<tr>
<td>Poor: &lt;5 words</td>
<td>37</td>
<td>48</td>
</tr>
<tr>
<td>Visual-manual coordination ****</td>
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<td></td>
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<tr>
<td>Postural level</td>
<td></td>
<td></td>
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<tr>
<td>25% - 75% percentile</td>
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<tr>
<td>Median</td>
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</tr>
<tr>
<td>25% - 75% percentile</td>
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</tbody>
</table>

*Age at which the first disturbances were recognized; **Parents' socio-professional category: Low (workers, farm workers); Average (middle class, employees, farmers); High (industrial, business, and intellectual professions, heads of company or business); ***Algorithm threshold; ****BL-R.
development of the child's understanding of the attempts by an adult to direct his attention towards an object and his abilities to understand and follow the adult's indication. Thus, the right response to most items was to look at and touch, to point to or take hold of what the adult had been attending to. To name and comment on objects in reply to an adult's questions appear when the child starts talking on the higher level in a series of 5 levels: simple, complex, conventional gestures, conventional verbal and symbolic utterances. 2) Initiation of joint attention.

The aim of this observation series was, firstly, to describe the child's growing awareness that an adult may attend to the same object or event as he himself is attending to, and, secondly, to describe the development of means which a child may use to direct an adult's visual attention to an object or event and make the adult attend to what he is himself just looking at. Such attempts, which must appear spontaneously, can also be divided into 5 levels.

In children with typical development the joint attention skill may be located between 6 and 12 months implying an interaction with others. It reveals itself in pointing and checking the direction of the other's glance, and among the precursors of these abilities is the capacity to detect the direction and target of another's glance. In children with autism this initial capacity is much retarded, and when they start walking the deficits they manifest with joint attention are remarked the most (Baron-Cohen, 1989; Jones & Carr, 2004; Nichols, 2005; Mundy, 2007). The response and initiation of joint attention are associated with the emergence of receptive and expressive language and deserve particular interest since their later development turns out to be a predictive variable in itself. The scores of the Vineland Scale (in months) and those of joint attention, distributed according to the three observation periods, are shown in Table 3.

Results

A technique for generalised linear models mixed with repeated measurements was used for data processing (Statistica, v-9). The regression was carried out in an exhaustive search for the best model and by crossing two criteria: the standardized AKAIKE information criterion (AIC) and the Bayesian de Schwarz-criterion. The explicative variables introduced into the model were as follows: the category of diagnosis, age at T1, age when the disorder was discovered, the parents' socio-professional category (SPC), sex, intensity of the disorder at T1, initial language level at T1, and the levels of adaptive behaviour at T1, T2, and T3. The values of the two explicative variables, at the three times, were also introduced into the model, and a descending procedure of a step-by-step nature was then undergone.

Regarding the response to joint attention, the prediction values brought about by the most satisfactory model (~ <5 words + >5 words. Autism + CARS + Phrases. T2 + Phrases. T3 + (1/NUM)) are shown in Table 4. The model for the variable to be predicted is not linear but of the Poisson family (log link) (see Table 4). The variables which seem to have a positive in-
fluence on the development of joint attention are the following:

Table 5. Prediction and behavioural initiation of joint attention.

|                         | Estimation | Standard errors | Value of z | Pr(>|z|) | Significance |
|-------------------------|------------|-----------------|------------|----------|--------------|
| Order at onset           | 2.79       | .15             | 18.2       | <2e-16   | 0.000        |
| <5 words                 | -69        | .08             | -8.08      | 6.68e-16 | 0.000        |
| >5 words’ Autism         | -46        | .09             | -5.28      | 1.27e-07 | 0.000        |
| Intensity                | -02        | .00             | -3.35      | -81e-5   | 0.000        |

AIC: 193.8; BIC: 211; LogLik: -91.9; Deviance: 183.8.

Several questions arise concerning the interpretation of these results. Among the factors retained, the majority of them appear to be risk or aggravating factors registered clinically as negative signs which forecast a delay or "non-appearance" of one or more skills: no productive language, most severe diagnosis, high disorder intensity. Only one of these factors is really specific for autism: that of the "typical autism" diagnosis; the other factors may be found in intellectual deficiency and/or in specific language disorders. Moreover, they all accompany global developmental delay. They are, however, extremely general markers and none of them belong in any specific way to the chain of development that leads to the complex coordination constituting joint attention (awareness of self, imitation, visual face-perception, selective attention, sharing, etc.) Yet they endorse the liaison between linguistic activity and joint attention.

Among the other variables introduced into the model, such as sex, levels of communication, socialisation or everyday adaptation, of which we might expect a somewhat close affiliation with the target variable, none of them had any predictive character. Thus we must admit that whatever methodological sophistication is used, we are left with extreme generalities: such as: an overall delay "produces" certain specific delays and/or is predictive of specific delays, except for small groups of children with certain language competences.

Perhaps these kinds of delay, like the qualitative impairments in development are, at the same time, the characteristics and the specificity of the autistic disturbance at the time of diagnosis. It is perhaps also the period in the development of the individual when the disturbance is the most pervasive, as it simultaneously affects major functions like communication and socialisation, and limits the taste for novelty—and, in so doing, limits the possibilities of prediction.

Conclusion

Should we then conclude that any prediction in autism is impossible? That the current formulation of the disorder, which is of a behavioural nature, is an epistemological obstacle for all prognostic activity, since the pathology is complex and developmental? Perhaps the normal approach, which consists of searching for precursor elements that may define PDD (limitation of interest, motor expressivity, proto-language), is not the best solution? It remains possible that today the very general markers are the best synthesis of these characteristics to come. The counterpart of this attitude is that we should not reduce autism spectrum disorder to a mere formulation of deficits. After all, autism is an original development, a queer construction, with astonishing ways of processing information, whether social or not, which may also lead to hypercompetences.

REFERENCES


