ORIGINAL ARTICLE

Prolongation of Brainstem Auditory-Evoked Responses in Autistic Probands and Their Unaffected Relatives

Michel Maziade, MD, FRCP(C); Chantal Mérette, PhD; Mireille Cayer, MSc; Marc-André Roy, MD, FRCP(C); Peter Szatmari, MD; Robert Côté, PhD; Jacques Thivierge, MD, FRCP(C)

Background: Brain function, as indexed by brain electrical activity, is heritable in humans, and it may be impaired in autism. Autism also has strong genetic determinants, and like all major psychiatric disorders, its complex clinical phenotype renders genetic studies difficult. Innovative strategies focused on alternative biological phenotypes are needed.

Methods: The early brain auditory-evoked response was assessed in 73 autistic probands and 251 relatives who were compared with 521 normal controls.

Results: We first confirmed in the autistic probands the presence of a slowing in nerve conduction in the auditory system as expressed by the prolongation of early brain auditory-evoked response under the form of I-III interpeak latencies (IPLs). Furthermore, we observed the same I-III IPL prolongation in the unaffected first degree relatives of the autistic probands compared with controls. Despite clear evidence of a coaggregation of autism and I-III IPL prolongation in families, the IPLs did not seem to be the sole liability factor for autism as suggested by the observation of 52% of families in which the autistic proband and relatives showed normal IPLs.

Conclusion: A prolongation of the early brain auditory-evoked response IPLs may be a marker for one of several deficits underlying autism and deserves further analysis as a potential alternative phenotype for the disorder.

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From the Centre de recherche Université Laval Robert-Giffard, Hôtel-Dieu du Sacré-Coeur de Jésus, Québec, Sainte-Foy, Québec (Drs Maziade, Mérette, Roy, Thivierge and Mrs Cayer); Department of Psychiatry, the Centre for Studies of Children at Risk, Chedoke-McMaster Hospitals, Hamilton, Ontario (Dr Szatmari); and the Département de mathématiques et statistique, Faculté des sciences et de génie, Université Laval, Sainte-Foy (Dr Côté).

AUTISM IS characterized by withdrawal and social deficits, communication abnormalities, stereotyped behaviors, and cognitive impairment. Genetic factors play a major role in autism[1,2] as indicated by a heritability greater than 90%.[3] Chromosomal abnormalities have been observed in cases of autism, particularly in sex chromosomes and chromosome 15q.[4,5] Recently, findings from genome screenings[6-9] have identified weak linkage signals, suggesting 14 loci potentially linked with autism with the highest probability for chromosomes 7q and 15q. However, because of the stoppage rule (the effect of having an autistic child reduces the number of subsequent children[10]) and because autistic persons are unlikely to reproduce, it is difficult to recruit the large number of multiaffected families needed to achieve sufficient statistical power for linkage analyses.[11] Therefore, alternative phenotypes or biological markers of susceptibility may help to detect the defective genes underlying autism. Two lines of evidence suggest that electrophysiological markers are logical candidates for such a role. First, prolonged early brain auditory-evoked response (BAER) has already been observed in autism.[12-17] These studies compare autistic subjects with normal controls.[12-16] In our population of Eastern Québec, we had already reported preliminary evidence of such early BAER prolongation in a small sample of 20 autistic subjects compared with mentally retarded subjects and normal controls.[17] Second, studies suggest genetic influences for brain electrical activity both in terms of background electroencephalogram and event-related potentials.[18] Consequently, the study of this activity may help to identify genetic influences on psychiatric disorders.

A good example is the finding of a decrease in the normal inhibition of the P50 auditory-evoked response in schizophrenic patients and their unaffected relatives, which is linked to a locus on chromosome 15q.[19,20] Such endophenotypes may represent a biological deficit in schizophrenia that could be more closely related to a single gene effect than schizophrenia itself. Similarly, autism could result from a combination of discrete neurophysiological deficits, and early BAER prolongation may be a marker of such a deficit.

SUBJECTS AND METHODS

SUBJECTS

The sample consisted of 73 autistic probands (mean [SD] age, 7.3 [5.1] years; 57 males) referred over a period of 8 years to the Hôtel-Dieu du Sacré-Coeur de Jésus (HDSC), the university regional child psychiatric hospital providing inpatient and outpatient services to the whole Québec City metropolitan area, Canada. Since autism has an estimated prevalence between 0.02% to 0.04%, and since subjects aged younger than 16 years were targeted (population, ≈200 000), the expected number of autistic patients was about 80. Our present sample of 73 may be considered as reasonably representative of the population of autistic patients in our region.

Our best estimate diagnostic procedure has been previously described.[17] Briefly, each subject had been diagnosed by 1 of 18 child psychiatrists at HDSC. Another psychiatrist, the principal investigator (J. T.), met all the patients and their parents to make a second best estimate diagnosis (*DSM-III-R*) according to all available clinical information. The longitudinal clinical observation in the present study extended for an average period of 4.0 years. When a disagreement occurred between the 2 diagnosticians, the case was not retained. The Autism Diagnostic Interview (ADI)[23] was not part of our best estimate method but was used to estimate symptom severity.

Additional measures were obtained by a research psychologist who met with all the parents to complete 2 instruments. First, the Vineland Adaptive Behavior Scale (VABS)[24] provides standardized measures of impairment for adaptive skills in socialization, communication, and daily living. The VABS is widely used and was standardized on a large population of children aged 2 to 18 years. It has high reliability and validity[24] and is sensitive to the deficits observed in autistic patients.[11,25] The mean (SD) VABS global score was 52.0 (15.4). Only one 15-year-old autistic subject (*DSM-III-R*) had a VABS score less than 20. Second, the ADI[23] is a standardized interview assessing 3 dimensions of autistic symptoms: social interaction (ADI-1), communication (ADI-2), and restricted/repetitive behaviors[26] (ADI-3). In our sample of autistic probands, the mean (SD) total ADI score was 32.2 (8.6). We applied 2 exclusion criteria: absence of wave components and presence of known neurological or ears, nose, and throat diseases directly implicating the brainstem or auditory nerve.

The relatives of 39 of 73 autistic probands had their BAER assessed. The results of the ADI and VABS for these 39 probands were not different from the results for the 34 other probands. We assessed 251 relatives (114 males) of these 39 probands: 106 first, 83 second, and 62 third degree relatives. The mean (SD) age of the relatives was 35.5 (16.5) years.

Normative IPL values had already been obtained in our laboratory in a group of 521 controls (255 males).[21,22] The controls were selected by advertisement and came from the same catchment area.[21,22] They completed a structured medical questionnaire, and subjects with any medical conditions were excluded. This sample was stratified by age (0-7 years, n=54; 8-13 years, n=130; and 14 years and older, n=337) and sex. The study was personally explained to the parents and relatives who signed a consent form.

BAER RECORDING

The procedure used in this study has already been reported.[17,21,22] The recordings were made in a soundproof Faraday cage. We used unfiltered rarefaction clicks (100 μs) in both right and left monaural stimulation (TDH-39 earphones; Telephonics, Farmingdale, NY) at a rate of 11.1 clicks per second for 2000 sweeps on the test and the retest. Prior to recording, the hearing level of both ears was tested in every subject. We used sensation levels (SLs) instead of normalized hearing levels to maximize the comparability of the data across subjects and between ears for the same subject. We used a 70 dB SL intensity level along with 30 dB contralateral white noise masking. The time base was 10 ms for 512 points (dwell time, 19 μs). The filter bandpass settings were 75 and 3000 Hz (filter slopes at 24 dB/octave). Cz was the recording site referenced to the ipsilateral mastoid.

In the group of autistic probands, whenever possible the hearing level of the child was determined, and a 70

Prolonged early BAERs indicate a slowing in nerve conduction within the auditory system and are thought to be related to impairments either inside (eg, neurinoma) or outside (eg, multiple sclerosis or pontocerebellar degeneration) this system. By convention, the consecutive early BAER waveform components are labeled sequentially by Roman numerals I to V (**Figure 1**). The intervals in milliseconds between 2 given waves, called interpeak latencies (IPLs), are designated by a hyphen between 2 waves (I-III or III-V).

The objectives of this study were to confirm the presence of prolonged early BAERs in a large sample of autistic probands and to search for the presence of a similar prolongation in the relatives of these probands with the hypothesis that such an anomaly might eventually serve as an alternative phenotype for genetic studies of the disease. Testing this condition was facilitated by the availability of 521 unrelated controls from the same population providing normative BAER values.[21,22]

RESULTS

INTERPEAK LATENCIES IN THE AUTISTIC PROBANDS

The typical BAER waveforms of an autistic and a control subject are illustrated in Figure 1. In the sample of probands (matched with controls; n=73 pairs), the mean of the differences in I-III IPL values was significantly greater than 0, meaning that autistic subjects had, on average, longer I-III IPLs than their matched controls (t_{72}=4.73, P<.001). Indeed, the histogram of the differences in I-III IPL values in the sample of probands showed a distribution that was clearly shifted to the right, (ie, not centered at 0) (**Figure 2**A). The I-V IPL was also significantly prolonged in autistic subjects (t_{72}=4.82, P<.001) but not the III-V IPLs (t_{72}=0.66, P=.51), suggesting that the significant difference in I-V IPLs was mainly due to the I-III component.

dB SL was used. This level had been used in our normative study.[21,22] In the other cases, the apparatus was set at 78 dB, which represents the mean setting on our equipment relative to a level of 70 dB SL in a group of 184 healthy children. In the group of relatives (children and adults), the level of 70 dB SL has always been used. For the sake of brevity, results are presented for the left ear. The results using the maximum IPL value from the 2 ears were also provided for the first degree relatives and yielded results similar to the left ear.

STATISTICAL ANALYSIS

The comparisons on IPL values of the autistic probands and their relatives to those of controls were adjusted for age and sex.[21,22] First, this was done by matching for age and sex each proband or relative with 1 of 521 available normal controls. The control subject with the closest age was chosen (mean [SD] age difference, 0.8 [1.4] years). If an experimental subject (either proband or relative) could be matched with more than 1 control, then 1 of them was chosen randomly. On the other hand, if no matching could be accomplished with a control within a 2-year age interval, then the experimental subject was excluded. This yielded 73 proband-control pairs and 217 relative-control pairs (first degree, n=94; second degree, n=82; third degree, n=41). The difference in IPL values was computed within each pair. A longer IPL value for the subject in the experimental group resulted in a positive difference. A paired *t* test was then used to test the null hypothesis of an average difference of 0. All statistical tests were 2-sided using a significance level of 5%.

Second, since in validity studies,[27,28] subjects exceeding the 95th percentile were considered as most likely to have an abnormal I-III IPL, a categorical approach was also used. The IPL values of control subjects allowed us to derive normative values adjusted for age and sex. Using these norms, each of 73 probands and 251 relatives were attributed a percentile based on their IPL rank within the appropriate age and sex category. The proportion of subjects exceeding the 95th percentile was computed within each of the different experimental groups. To test the null hypothesis of independence in risks between subjects in an experimental group and controls, χ^2 statistics on 2×2 tables were used. For the probands, an odds ratio was computed with the corresponding 95% confidence interval (CI), as it is done in typical case-control studies. For the relatives, risk ratios (RRs) were calculated because in such a family study, being a relative of a case patient is similar to being exposed to a risk factor; therefore, data can be treated as in a cohort study situation.[29]

Given that subjects within families are not independent of one another, the 95% CI computed for the RR for relatives may not be valid, though the test of independence (hence, the *P* value) remains valid.[29] Therefore, in addition to computing RRs and 95% CIs in relatives classified according to their degree of relatedness, the sample of relatives was also stratified into subsamples of independent observations: (1) the parents (n=71); (2) the youngest sibling per family (n=19); (3) the eldest sibling per family (n=19); (4) the youngest maternal and paternal second degree relatives (n=30); (5) the oldest maternal and paternal second degree relatives (n=30); (6) the youngest maternal and paternal third degree relatives (n=15); and (7) the oldest maternal and paternal third degree relatives (n=15). The reason for selecting the oldest or youngest person within a class of relatives was to obtain nonrandom subsamples of subjects and, thus, be able to easily replicate our results.

Familial resemblance of the I-III IPL percentile of family members was assessed using hierarchical regression,[30] which allows for fixed and random effects. We fitted a 2-level model in which the first and second level consisted respectively of the family members and the families. A likelihood ratio test was carried out for testing the significance of the effect of families by comparing the 2-level model with the model omitting the families (level 2). This yielded a χ^2 statistic with 1 *df*. Familial resemblance was assessed in 3 samples: (1) probands and first degree relatives (n=138 family members; 39 families); (2) probands and first plus second degree relatives (n=221 family members; 39 families); and (3) all family members (n=283 family members; 39 families).

The cumulative and relative frequency distributions of the I-III IPL percentile ranks in autistic probands were also clearly shifted to the right compared with controls (**Figure 3**). The odds of exceeding the 95th percentile in probands compared with controls were 5.64 (95% CI, 3.10-10.28; $P<.001$).

We thus confirmed a prolongation of I-III IPL in the 73 autistic probands vs controls. There was no significant correlation between the IPL in the probands and severity of the autistic characteristics on each of 3 ADI subscales and the VABS (n=67: for ADI-1, $r=0.04$, $P=.76$; for ADI-2, $r=0.01$, $P=.94$; for ADI-3, $r=0.21$, $P=.09$; for VABS, $r=0.05$, $P=.66$).

IPLs IN RELATIVES

The first degree relatives also presented significantly longer I-III IPLs than matched controls (n=94 pairs, $t_{93}=2.36$, $P=.02$; Figure 2B). No significant I-III IPL prolongation was found in second (n=82 pairs, $t_{81}=1.16$, $P=.25$) or third degree relatives (n=41 pairs, $t_{40}=0.81$, $P=.43$). There was no significant evidence of a prolongation in I-V IPLs in first, second, or third degree relatives (see note in Figure 2B).

In our stratified subsamples of independent observations, siblings had significantly longer I-III IPLs than controls (n=19 pairs, $t_{18}=2.48$, $P=.02$ for youngest siblings; n=19 pairs, $t_{18}=3.25$, $P=.004$ for eldest siblings). Parents however did not have significantly longer I-III IPLs than controls (n=71 pairs, $t_{70}=1.61$, $P=.11$ for parents; n=33 pairs, $t_{32}=0.60$, $P=.55$ for fathers; n=38 pairs, $t_{37}=1.69$, $P=.10$ for mothers). No evidence of an I-III IPL prolongation was found in second or third degree relatives (n=30 pairs, $t_{29}=0.84$, $P=.41$ for youngest second degree relative; n=30 pairs, $t_{29}=0.84$, $P=.41$ for oldest second degree relative; n=15 pairs, $t_{14}=1.03$, $P=.32$ for youngest third degree relative; n=15 pairs, $t_{14}=-1.62$, $P=.13$ for oldest third degree relative).

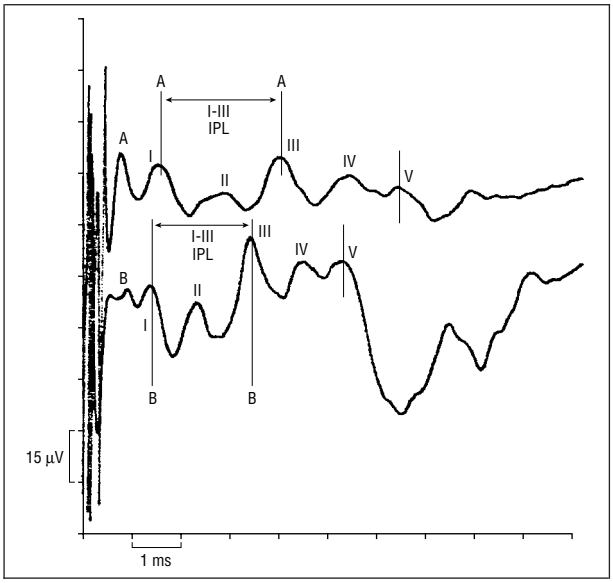

Figure 1. *The typical slowing (in milliseconds) of the early brain auditory-evoked response of an autistic proband (A) compared with a normal control (B). IPL indicates interpeak latencies.*

The cumulative frequency distribution of the I-III IPL percentile ranks in unaffected relatives lay between that of the autistic probands and the controls (Figure 3A). In first degree relatives, the risk of having an I-III IPL exceeding the 95th percentile was 2.1 times greater than in controls ($P=.007$; **Table**). The RRs were also significantly greater than one for parents (RR=2.2, $P=.015$), youngest siblings (RR=3.7, $P=.002$), and eldest siblings (RR=3.7, $P=.002$), but they did not consistently reach significance level in second or third degree relatives (Table). Among the 11 parents who exceeded the 95th percentile, there were 5 fathers and 6 mothers. When we characterized the first degree relatives by the highest I-III IPL values from 2 ears, results remained similar (RR=2.39; 95% CI, 1.08-5.27; $\chi^2_1=5.54$; $P=.019$).

FAMILIAL RESEMBLANCE OF THE I-III IPL TRAIT

According to the likelihood ratio test, the effect of families was significant in each of 3 overlapping samples of family members, meaning that the IPL trait showed significant familial resemblance ($\chi^2_1=5.41$, $P=.02$ with first degree relatives; $\chi^2_1=7.18$, $P=.007$ with first and

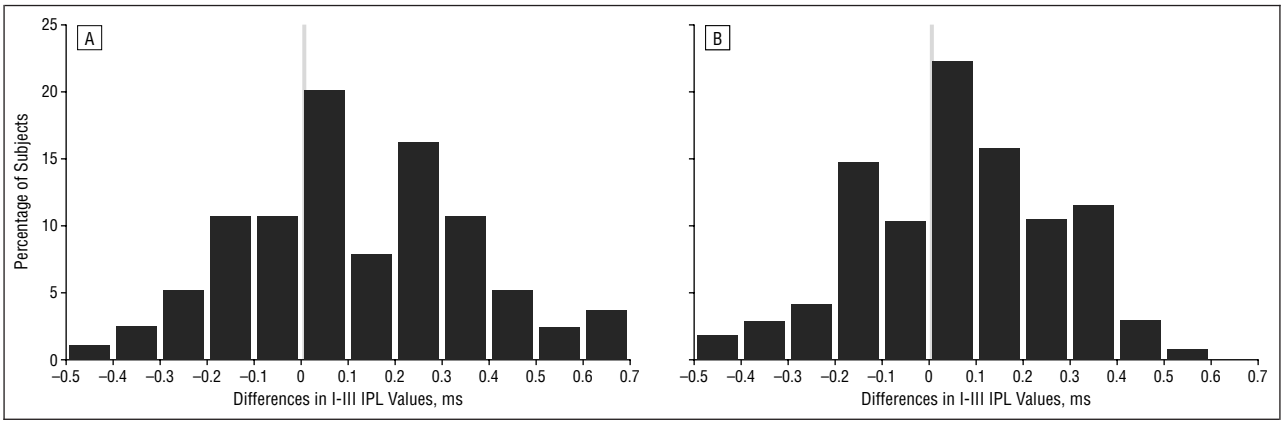

Figure 2. *A, Autistic probands paired with normal controls (n=73 pairs), and B, autistic probands' first degree relatives paired with normal controls (n=94 pairs). Each proband and first degree relative was paired with a normal control of closest age and same sex, then the difference in interpeak latency (IPL) values was computed within each pair. A positive difference indicates that the probands (A) or relatives (B) had longer I-III IPLs than the matched control. The figures show that the distribution of these differences is clearly shifted to the right (ie, not centered at 0). There was no significant evidence of a prolongation in I-V IPL (not shown in Figure 2) in first degree relatives ($t_{93}=-0.27$, P=.79); second degree relatives (n=82, $t_{81}=1.04$, P=.30); or third degree relatives (n=41, $t_{40}=0.93$, P=.36).*

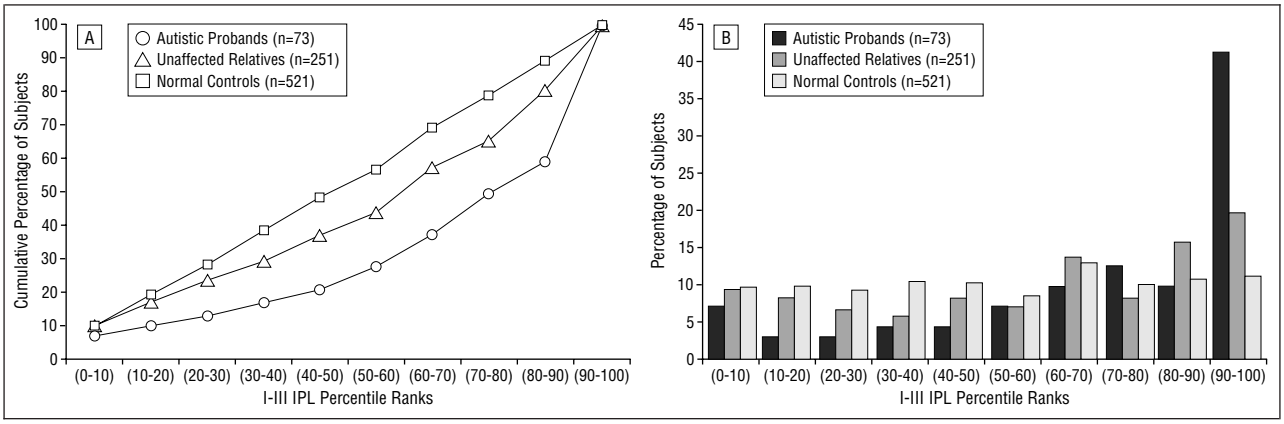

Figure 3. *A, Cumulative frequency distributions of the I-III interpeak latency (IPL) in percentile ranks, and B, relative frequency distributions of the I-III IPLs in percentile ranks. Each proband or relative was assigned a percentile rank based on normative values from his/her age and sex category. A, Cumulative frequency distributions of these values for the group of probands, unaffected relatives, and normal controls. The I-III IPL of the relatives occupy an intermediate position between those of the autistic probands and the controls. B, Corresponding relative frequency distributions. As many as 79% of the autistic probands displayed a percentile rank above the median.*

Risk of Exceeding I-III Interpeak Latency 95th Percentile in Relatives of Autistic Probands Compared With Normal Controls According to Degree of Relatedness*

Degree of Relatedness	N	Risk (%) of Exceeding 95th Percentile†		Risk Ratio	95% CI	χ^2 (*df* = 1)	*P*
		Relatives of Autistic Probands	Controls‡ (N = 521)				
First degree relatives	106	15.1	7.1	2.1	1.18-3.84	7.3	.007
Parents	71	15.5	7.1	2.2	1.12-4.26	5.9	.015
Youngest siblings	19	26.3	7.1	3.7	1.46-9.40	9.4	.002
Eldest siblings	19	26.3	7.1	3.7	1.46-9.40	9.4	.002
Second degree relatives	83	14.5	7.1	2.0	1.06-3.91	5.2	.02
Youngest§	30	10.0	7.1	1.4	0.43-4.59	0.4	.55
Oldest§	30	26.7	7.1	3.8	1.76-8.04	14.5	<.001
Third degree relatives	62	9.7	7.1	1.4	0.58-3.21	0.5	.46
Youngest§	15	6.7	7.1	0.9	0.13-6.88	0	.95
Oldest§	15	0	7.1	0	NA	1.1	.28
First to third degree relatives	251	13.6	7.1	1.9	1.19-3.06	8.4	.004

*CI indicates confidence interval; NA, not applicable due to a null risk ratio.
†Each subject was assigned a percentile rank based on normative values.
‡Proportions in controls slightly exceed the expected 5% due to the presence of equal I-III interpeak latency values within age and sex category.
§In each family, up to 2 independent observations could be used: 1 maternal and 1 paternal relative.

second degree relatives; χ^2_1=8.28, *P*=.04 with all family members).

Examples of pedigrees showing familial resemblance are shown in **Figure 4** in which I-III IPL percentiles are indicated for each family member. Families R2 and R5 are examples in which both the proband and several relatives tended to have high percentile ranks. Family RD is one in which percentile ranks tended to be low. Despite an evidence of familial resemblance, we observed a proportion of families in which the proband alone had a high I-III IPL value (family RE) and some in which a parent and a few other relatives showed a high IPL value but not the autistic child (family R4). Using the 95th percentile as a cutoff, we found that 30% of the autistic probands had at least 1 parent with prolonged IPL, and 48% of the families had either the proband or a parent or both with a prolonged IPL.

COMMENT

We confirmed in a large sample of autistic patients the presence of a slowing in nerve conduction in the auditory system as expressed by the prolongation of early BAERs and I-III IPLs. Moreover, we now observe the same I-III IPL prolongation in the unaffected first degree relatives of autistic subjects and a familial resemblance of the IPL trait within families. The IPL prolongation is not the first biological anomaly to be found in unaffected relatives of autistic probands. Previous reports have shown that these relatives have other biological peculiarities either in terms of immunopathologic indices such as decreased plasma concentration of the C4B protein[31] or an increased frequency of the B44-SC30-DR4 haplotype,[32] or in terms of biochemical indices such as hyperserotoninemia.[33-36]

We made 5 observations suggesting a complex relationship between IPL and autism. First, even though a significant association between the IPL marker and autism was observed, the deficit expressed by the IPL prolongation may not account for all cases of autism. Indeed, there were roughly 50% of the families in which neither the proband nor the parents showed an IPL prolonged greater than the 95th percentile. This implies that the IPL prolongation as a marker of a neuropathologic process would not be necessary to develop autism and would not consequently be the sole liability factor for autism. Hence, etiologic heterogeneity and possibly genetic heterogeneity would be likely for autism. Second, none of the relatives with extreme IPL expressed the autistic phenotype. This implies that the IPL prolongation would not be sufficient to develop autism, suggesting reduced penetrance and consequently, the need for IPL to interact with other genetic or environmental factors to be expressed as autism. Third, a proportion of autistic probands did not display a prolongation whereas at least one of their parents did. This may be due to pleiotropy (ie, the phenomenon in which a genetic latent trait can be expressed in 2 independent phenotypes, as was proposed by Holzman et al,[37] to model the relationship between abnormal eye tracking and schizophrenia). Fourth, some probands carried the IPL prolongation, whereas their parents did not. This could reflect an increase in trait severity across successive generations, suggesting anticipation. Fifth, our data did not suggest a sex-linked transmission given the absence of an excess of transmission from the maternal or paternal side.

As well exemplified for schizophrenia and P50 anomalies,[20,38] the present observation of IPL slowing in autism and in relatives of subjects with autism justifies further investigations of early BAER prolongation as a potential alternative phenotype for autism. Such an alternative phenotype could increase the statistical power of genetic analyses in autistic pedigrees by increasing the number of affecteds. Besides, the observed complex relationship between autism and IPL suggests that autism might consist of a combination of neurophysiological deficits and that IPL prolongation could be a marker of one

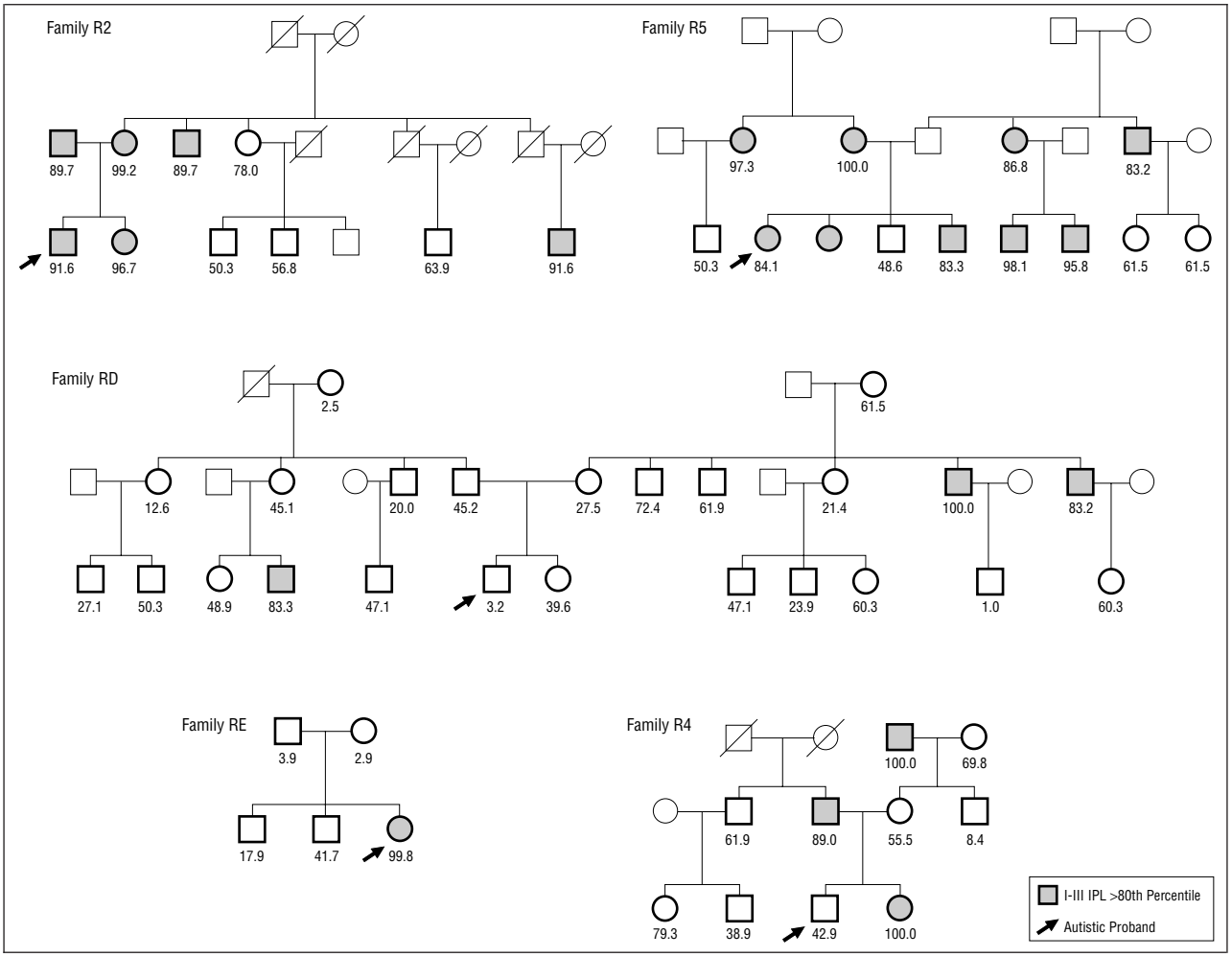

Figure 4. *The I-III interpeak latency (IPL) percentile value is indicated for each family member. The autistic probands are marked with an arrow. To facilitate the observation of higher values, the I-III IPLs higher than the 80th percentile are shaded.*

of these. The IPL could then show a simpler genetic transmission than autism itself and, therefore, be the target of further biological and genetic investigation.

Because much remains to be known about the neural generators of BAER waveforms, it is difficult to define the link between BAER and autism. Brainstem auditory-evoked responses might however be related to 3 kinds of neurobiological parameters reportedly associated with autism: (1) myelination, (2) cerebellum neuroanatomy, and (3) serotonin. First, myelination can be a target because of its implication in nerve propagation. Using magnetic resonance imaging to assess myelination status in children with developmental delays, Harbord et al[39] reported abnormally prolonged BAER in children with diminished myelination, suggesting an association between increased and abnormal myelination. Second, cerebellum degenerative or tumoral diseases[40-42] were found to be related to waveform BAER amplitude and latency values. In this regard, it is difficult not to evoke the description by Courchesne et al[43-46] of cerebellar lobules VI and VII hypoplasia in autistic patients. Third, hyperserotonemia is the best replicated biochemical abnormality in autistic patients[47-51] and their relatives.[33-36] In that respect, serotonin has been found to stop axon elongation for synapse formation of particular neurons.[52]

Piven et al[53] found in the parents of autistic probands the presence of a broad or lesser autistic phenotype (ie, parental personality characteristics of aloofness, rigidity, hypersensitivity to criticism, speech, and language deficits). Only a proportion of families presented this lesser phenotype. We intend to evaluate such a lesser phenotype[53] in unaffected relatives with the hypothesis that the relatives with extreme IPLs will be more likely to display the lesser clinical variant than those below the IPL median. If this hypothesis is confirmed, analyses of the segregation and/or cosegregation of the IPL and the autistic (or autistic-like) phenotypes in the pedigrees will be possible and will hopefully facilitate genetic linkage analysis of autism or the IPL endophenotype.

The present study has limitations. First, because of the small number of autistic subjects in a pedigree, it was impossible to look at the cosegregation of the illness with the electrophysiological deficit. Second, even though the present sample constitutes a relatively large family collection for autism, the numbers in the subsamples had limited power. Third, the present findings apply only to autism and not to other forms of pervasive developmental disorder that have been shown to be related to autism in family studies.[54,55]

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Corresponding author: Jacques Thivierge, MD, FRCP(C), or Michel Maziade, MD, FRCP(C), Centre de recherche Université Laval Robert-Giffard, 2601, chemin de la Canardière, Beauport, Québec G1J 2G3 Canada (e-mail: michel.maziade @psa.ulaval.ca).

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