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Neuromotor functions in Inuit preschool children exposed to Pb, PCBs, and Hg

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Abstract

The aim of this study was to examine the effects of prenatal and postnatal chronic exposure to mercury (Hg), polychlorinated biphenyls (PCBs) and lead (Pb) on the neuromotor development of preschool children. The study population consisted of 110 preschool Inuit children from Nunavik (Canada). Blood Hg, PCBs and Pb concentrations were measured at birth (cord blood) and at the time of testing. Gross motor functions were evaluated and a neurological examination was performed. Fine neuromotor performance was assessed using quantitative measures of postural hand tremor, reaction time, sway oscillations, as well as alternating and pointing movements. Potential covariates were documented including demographic and familial characteristics, other prenatal neurotoxicants (alcohol, tobacco) and nutrients (selenium (Se), Omega-3 polyunsaturated fatty acids (n-3 PUFA)). Hierarchical multivariate regression analyses were performed, controlling for significant covariates. Gross motor development was not linked to prenatal exposures. However, significant associations were observed between blood Pb concentration at testing time and changes in reaction time, sway oscillations, alternating arm movements and action tremor. For some of these outcomes, neuromotor effects of Pb exposure are observed at blood concentrations below 10 μg/dl. Negative effects of PCBs on neuromotor development were not clearly observed, neither were the potential beneficial effects of n-3 PUFA and selenium. Tremor amplitude was related to blood Hg concentrations at testing time, which corroborate an effect already reported among adults.
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1. Introduction

Methylmercury (MeHg), organochlorine compounds (OCs) and lead (Pb) are recognized as significant environmental neurotoxic agents. In Nunavik (Northern Quebec, Canada), chronic exposure to these contaminants occurs mainly through consumption of traditional foods such as fish, marine mammals, and sea bird eggs [34]. However, the consequences of exposure to these pollutants have not been examined in Inuit children.

Cognitive and motor development in children have been examined in several populations exposed pre- and postnatally to these neurotoxicants but results have varied considerably. Several factors could be responsible for differences between studies including: the sensitivity of

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the outcomes examined, the source and level of exposure, the characteristics of the populations, and the covariates examined. Neuromotor performance has not been extensively studied in previous reports, despite the fact that motor skills are important in the child's daily activities. Moreover, the use of quantitative instrumentation has been rarely used in these studies in order to measure neuromotor functions precisely.

1.1. Organochlorine compounds (OCs) and psychomotor development

Polychlorinated biphenyls (PCBs) and chlorinated pesticides are organochlorine compounds. Developmental deficits have been related to prenatal exposure to these neurotoxicants. Low to moderate prenatal PCB exposure has been related to a decrease in psychomotor development during the first months of life [20,25,40]. Negative effects of prenatal OC exposure have been reported during childhood [22,28,29,36,45,46]. In a group of 7- to 12-year-old children born to PCB exposed Taiwanese mothers, Chen and Hsu [11] did not report did observe anomalies on the standard neurological examination but did observe subtle signs consisting of mirror movements, mild to moderate deficits in finger-thumb opposition, and choreiform movements. However, results on neurological functions have been inconsistent between studies. In a recent study, Daniels et al. [14] did not observe a relation between prenatal PCB exposure and children's mental or psychomotor scores within the general population of the United States but this study was conducted with infants exposed to background levels.

1.2. Mercury (Hg) and psychomotor development

Most of the available evidence suggests an effect of prenatal exposure to Hg on long term motor development. Harada [24] reported that children from Minamata Bay born from mothers who had consumed Hg-contaminated fish during pregnancy presented severe psychomotor retardation. Abnormal neurological signs were also related to maternal ingestion of Hg-treated seed grains in Iraq [32]. In the Canadian Cree population, the presence of abnormal muscle tone and deep tendon reflexes have been associated with increased maternal Hg exposure in boys [33]. Moreover, Cordier et al. [13] reported a dose-dependent association between maternal hair Hg concentrations and increased deep tendon reflexes, poorer legs coordination, and poorer performance on visuo-spatial organization (Stanford-Binet Copying score). In the Faroe Islands, Grandjean et al. [21] found that, in 7-year-old children, prenatal mercury was mostly related to cognitive functions and to a lesser extent to motor functions. In a recent publication involving the Seychelles cohort study [35] Myers reported that prenatal Hg exposure was associated with a non optimal performance in fine motor functions (grooved pegboard) in boys at 9 years of age. The authors however concluded that this association was maybe due to chance.

1.3. Lead (Pb) and psychomotor development

Low-level postnatal Pb exposure has been associated with adverse effects on visuo-motor integration [2] and fine motor skills [18,47] during childhood. Wasserman et al. [47] reported that blood Pb levels (averaged from child's birth to age 4.5 years) were associated with poorer fine motor and visuo-motor function but unrelated to gross motor coordination. In 6-year-old children from Cincinnati, Dietrich et al. [18] found that neonatal and postnatal blood Pb levels were significantly associated with poorer scores on measures of upper limb speed and dexterity, and fine motor skills. Within an environmental health screening program in Germany, Winneke et al. [49] found that low blood Pb levels were associated with a decrease of maximal finger tapping speed and a deficit in pattern recognition while simple reaction time was not affected. This cohort of 6-year-olds was exposed to lower Pb levels than cohorts of previous studies.

2. Objectives

The literature to date suggests that there is a need for more data on the long term consequences of exposure to environmental contaminants on neuromotor functions in children. We evaluated neurological status, reaction time, alternating and pointing arm movements and balance in different conditions using sensitive tests designed to detect sub-clinical neuromotor effects. The main goal of this study was to investigate neuromotor effects in preschool Inuit children exposed to the following environmental neurotoxicants: mercury (Hg), polychlorinated biphenyls (PCBs) and lead (Pb). A second goal was to discriminate the effects of prenatal exposure from those related to exposure during childhood. Thirdly, the possible beneficial effects of nutrients present in fish and marine mammals, omega-3 polyunsaturated fatty acids (n-3 PUFA) and selenium (Se), were also examined.

3. Methods

3.1. Participants

This study was conducted as a follow-up of the Cord Blood Monitoring Program which took place in Northern Quebec (Canada), a region called Nunavik, between 1993 and 1996. The women who had participated in the first phase of the study, which took place at the time of birth of their child, were included in the present study [17]. The following inclusion criteria were used for entry into the study: children between 4 and 6 years of age, biological mother as primary caretaker, full-term pregnancy, birth

weight at least 2500 g, no known neurological or developmental disorder, and no severe chronic disease. Eligibility was first determined through database information, followed by a parental interview and a review of the medical records. From the 483 participants of the Cord Blood Monitoring Program, 228 were eligible for this study. The main reason for exclusion was that the child was adopted at birth (24.2%). Given that the consent to participate to the Cord Blood Monitoring Program was obtained from biological mothers, we did not invite the adoptive mothers to participate in this study. A significant number of children (14.5%) were eliminated because they were not in the age range for testing at the time of the data collection, which was from 58 to 71 months of age. Other reasons for exclusions were death or health problems of mother or child (2.4%), missing information on exposure or identification (9.9%), or the family moved out of the participating communities (1.4%).

From the 228 eligible participants, 32.0% could not be reached by our research assistants and 25.7% refused to participate. The main reason for refusal to participate was the obligation to travel to another community for child testing. A total of 110 children were tested. Informed consent was obtained from all participating mothers. The study participants were living in villages from the Hudson (48.2%) and Ungava coasts (51.8%). Descriptive data for the 110 families, of which the study sample was comprised of, are presented in Table 1.

In order to assess potential bias, *t*-tests were performed to compare participants (n=110) to 1) excluded subjects (n=326), 2) eligible non participants (refusals, unable to contact: n=118), and 3) refusals (n=38). Results revealed no significant differences between groups on the following variables: age of the mother at testing time or at delivery, parity, number of cigarettes smoked per day during pregnancy, child's weight at birth (gr), duration of gestation (nb of days), cord blood concentrations of PCBs, pesticides, Hg and Pb. Thus the sample was representative of the population.

3.2. Biological measures and laboratory procedures

Umbilical cord blood sample was used to document prenatal exposure to PCBs, chlorinated pesticides, Hg and Pb. Child's blood and hair samples were collected to quantify PCBs, chlorinated pesticides, Hg and Pb exposures at the time of neuromotor evaluation. The analyses were performed at the Laboratoire de Toxicologie INSPQ, which is accredited by the Canadian Association for Environmental Analytical Laboratories. Quality control procedures were described previously [39]. The 14 most prevalent PCB congeners (IUPAC nos. 28, 52, 99, 101, 105, 118, 128, 138, 153, 156, 170, 180, 183, 187) and 11 chlorinated pesticides or their metabolites (Aldrin, α-chlordane, γ-chlordane, pp′-DDT, pp′-DDE, HCB, β-HCH, mirex, *cis*-nonachlor, *trans*-nonachlor, oxychlordane) were measured in cord and child plasma samples. Concentrations were measured in the purified extracts using high-resolution gas chromatography (Hewlett-Packard HP5890A), with two capillary columns (Hewlett-Packard Ultra I and Ultra II) and dual Ni-63 electron capture detectors. Hg concentrations were determined in cord and child blood samples as well as in the hair

Table 1
Characteristics of study sample

	Total *N*	Mean	SD	Range	*N*	%
Child						
Age (years)	110	5.4	0.4	4.8–6.2		
Gender (% male)	110				50	44.6
Height (cm)	107	110.1	4.4	101.3–126.1		
Weight (kg)	106	21.5	3.3	16.3–44.4		
Head circumference (cm)	106	52.0	1.2	48.9–54.5		
Iron-deficient[a]	110				6	5.4
Family						
Maternal age (years)	110	30.2	5.4	21.4–45.1		
Marital status (% single)	110				23	20.9
Parity	109	4.3	2.0	1.0–10.0		
Education (years)	110	9.0	2.2	5.0–16.0		
Socioeconomic status[b]	107	28.4	1.2	8.0–57.0		
Proportion working mothers	110				74	67.3
Language of mother interview	110					
English					93	84.5
French					6	5.5
Inuktitut					11	10.0
Breastfeeding (%)	108				86	79.6
Duration (months)[c]	86	16.7	1.8	0.1–60.0		

[a] Hemoglobin ≤ 105 g\l.
[b] Hollingshead index for the mother and her partner or, if she was not self-supporting, for her primary source of support (usually her parents).
[c] For breastfed babies only.

sample (5-mm diameter and 1-cm length) collected at testing time, using atomic absorption spectrometry (Pharmacia Model 120). Pb concentrations were analyzed in cord and child blood by graphite furnace atomic absorption with Zeeman background correction (Perkin Elmer model ZL4100). Detailed laboratory procedures are presented elsewhere [34,39]. For any neurotoxicants not detected in blood or hair, half the detection limit was attributed. The detection limit was 0.2 μg/l (1.0 nmol/l) for blood mercury, 0.2 μg/g (1.0 nmol/g) for hair mercury, 1.04 μg/dl (0.005 μmol/dl) for Pb and 0.02 μg/l for all PCB congeners and chlorinated pesticides [34].

3.3. Equipment and test procedures

The Nunavik region is located in arctic Quebec (north of the 55th parallel). Inuit live in 14 villages along a 2000 km shoreline. Data collection, which involved testing children and interviewing mothers, was performed between January 2000 and October 2002, and consisted of five 1-month trips to Nunavik. Maternal interviews were conducted by a psychologist with previous experience with the Inuit. English was the principal language used during these interviews (93 women). French was also used with 6 women, and an Inuit interpreter (English–Inuktitut translation) was required for 11 women. Neuromotor evaluations were performed by a physical therapist while a trained assistant was in charge of data acquisition on the computer. Both child testers were PhD students in neuropsychology. Child testing sessions were conducted with the help of an Inuit interpreter since Inuktitut was the maternal language of most preschoolers. This Inuit interpreter was trained on testing procedures and instructions. For the neurological examination, the physical therapist was trained by a neuropediatrician. Assessment of motor functions lasted about 1 hour and was conducted at the beginning of the overall testing session which included the assessment of cognitive and visual evoked potentials [41]. The two PhD students were blind with respect to exposure to environmental contaminants.

Neurological function was measured with the Amiel-Tison and Gosselin examination [1], which is an objective neurological examination using standardized procedures evaluating parameters such as posture and passive tone at rest, reflexes and postural reactions, and overlapping of cranial sutures. Gross motor functions were examined using 10 motor tasks developed by Huttenlocher et al. [27]. These tasks included walking on toes and on heels, walking on a line forward and backward, hopping on one foot as well as a simple and complex tapping reproduction tasks (tap 5 times with one hand; tap alternatively with left and right hand for 4 cycles; tap twice with left hand then twice with right hand for 5 cycles; tap once with left hand and twice with right hand for 5 cycles). The assessment also tested the child's ability to remain motionless for 1 minute, hand coordination, and downward arm drift.

3.3.1. Quantitative tests

Specific motor functions were assessed with quantitative tests used for sub-clinical detection of movement disorders. All the selected instruments were originally designed for adult motor assessment [4,5,16]. They were adapted for children by adding visual or auditory reinforcements and by slightly modifying the procedures (recording time, position adopted). These adaptations were established in order to keep the interest of children and thus optimize their participation throughout the evaluation. Normative data were obtained in healthy preschool children from an urban area using the adapted procedures. The following dimensions of neuromotor function were assessed: postural hand tremor, reaction time, standing postural sway oscillations, rapid pointing movements and rapid alternating movements.

The Catsys system developed by Danish Product Development (Snekkersten, Denmark) was used to record postural hand tremor, reaction time and postural sway. Postural hand tremor [13,19] was measured during 8 seconds while children held a light stylus at approximately 10 cm in front of their navel, with the elbow joint bent at a right angle and without body contact. During recording, children were asked to look at the tip of the stylus, breathe normally and relax. We added a visual stimulus (a monkey face with mobile eyes) on the stylus to encourage children to stay still during the recording. Reaction time to an auditory stimulus was assessed using a hand-held switch activated with the thumb [15].

The Sway Analysis Test System is a platform containing three orthogonal strain-gauge devices [14]. Postural sway was tested by asking the children to stand on the platform with their feet 1 cm apart and with their arms at their sides. Children were asked to look at a picture placed at 2 m in front of them, or to keep their eyes closed. Postural sway was measured for 23 seconds eyes opened and 23 seconds eyes closed (static conditions), 10 seconds on one foot and 10 seconds in tandem (heel to toes) position (balance conditions).

Rapid pointing movements were recorded with the Eurythmokinesimeter (DOCO Microsystèmes Inc, Montreal, Canada) [4], which measures the speed and precision of contacts between a hand-held stylus and 2 targets, one proximal, one distal, made of four concentric rings. Children sat in front of the system at a distance such that the arm of the child was almost completely extended when touching the distal target. Children were asked to strike the central area of the targets in alternation as quickly and as precisely as possible, starting with the proximal target. The test was performed for 20 seconds with each hand. The sampling frequency of data acquisition of the system was 500 Hz.

Rapid alternating arm movements (RAMs) were measured with the Diadochokinesimeter (DIADO) (DOCO Microsystèmes Inc, Montreal, Canada) [5], which records angular displacement over 7 seconds during pronation–supination movements of the forearms. Children were asked to hold a foam ball in each hand and to rotate them while

keeping the elbows close to the trunk and flexed at 90°. The rotation of the balls was recorded by optical encoders (resolution: 0.18°, sampling frequency: 200 Hz). Three conditions were tested twice: 1) rotation of the right hand with the left hand kept immobile in neutral position, 2) rotation of the left hand with the right hand immobile, 3) symmetric rotation of both hands. The dependent variables used in the analysis are described in Table 2.

Children were first familiarized with the instrumentation, and practice trials were always performed before the recording of the test. The same equipment was used for all children during the entire study. Calibration of the instruments was performed by the manufacturer before the start of data collection. The diadochokinesimeter (DIADO) and eurythmokinesimeter (EKM) were inspected by the manufacturer three times during data acquisition to ensure the fidelity of the measures. Moreover, an overall examination of the data showed no evidence of drift of the neuromotor performances over time (measured with regression analyses, controlling for covariates). This observation is important since testing was performed over a 2-year period. Pre-testing trials were done before the beginning of each child evaluation and the setting of zero points was done just before each recording. Graphic visualization was obtained immediately after data recording.

Table 2
Definitions of the characteristics selected for the analyses

Rapid alternating movements of the forearms (DIADO)[a]	
Velocity	Mean velocity for each cycle average over all cycles (degrees/second). Larger values indicate faster movement.
Coeff. of variation	Standard deviation of all diado characteristics normalized. The larger the number score the more irregular the performance.
Synkinesis	Associated contralateral movements observed when one hand is moving.
Coherence between hands	Reflects the similarity of the oscillations in the two hands. A high coherence value means that the two hands are synchronized.
Precise and rapid pointing movements (EKM)[b]	
Tremor	Measures the number of extra contacts after the initial one when there are multiple contacts on a target area.
Irregularity	Standard deviation of intervals between events. The lower the number score, the more regular the performance.
Contact duration	Average of total duration of contacts on the targets. The lower the number score, the shorter the contact and the better the performance.
Reaction time[c]	
Average reaction time	Mean of all reaction times obtained during the 50 second time test.
Postural sway (eyes open, closed, one foot and tandem position (heel to toes))[c]	
Sway velocity	Average travel speed of the force centre in the horizontal sway plate plane (mm/s).
Sagittal sway	Simple mean of the recorded y-direction values of the force centre in a coordinate system (mm).
Transversal sway	Simple mean of the recorded x-direction values of the force centre in a coordinate system (mm).
Arm postural tremor[c]	
Tremor intensity	Root mean square of acceleration recorded in the 0.9–15 Hz band (m/s^2). Larger values indicate larger tremor amplitude.
Harmonic index	Compares the tremor frequency pattern with the pattern of a single harmonic oscillation which as a HI=1.00. A regular tremor has a higher harmonic index (e.g. pathological tremor).

[a] [4].
[b] [5].
[c] [16].

3.4. Potential confounding variables

A broad range of potential confounding variables was documented. These variables were selected for their potential or documented associations with the dependent variables. To document possible beneficial effects of nutrients against neurotoxicants, concentrations of selenium (Se) and n-3 PUFA (docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA)) were obtained from laboratory analyses conducted on umbilical cord and child blood samples. Laboratory procedures were previously described in Muckle et al. [34].

Maternal interviews allowed documentation of socio-economic status, highest grade achieved by the primary caregiver, number of children and adults at home, maternal psychological distress (IDESQ questionnaire validated in the Santé Québec Inuit Health Survey) [37], maternal non verbal reasoning abilities (Raven Progressive Matrices) [38], intra-family violence (Conflict Tactics Scales) [42]. The quality of intellectual stimulation provided by the family was assessed with the HOME Inventory for families of preschoolers [9]. Maternal reproductive history (e.g. number of previous abortions and stillbirths, parity) was also documented. Prenatal exposure to alcohol (frequency and quantity), illicit drugs (frequency) and tobacco (number cigarettes/day) were documented at the time of the maternal interview. Iron deficiency at time of testing was documented from hemoglobin levels in the child's blood sample.

3.5. Statistical analyses

As a data screening procedure, all data exceeding 2 standard deviations from the mean were examined. Some participants had to be discarded from the analyses because their performance on some tests was considered invalid. Three criteria were selected to characterize invalid data: lack of comprehension of task instructions, failure to complete the task, and lack of cooperation during the task. Because the cooperation of some children varied from one task to another, a participant could be eliminated for one task but not for the next task. All other outliers were kept in the database. Analyses were first performed with all available data included, and then without outliers. The analyses with

and without outliers led to the same statistical outcomes in all but one endpoint (see Results section). In all cases, we reported the models with the outliers. In order to normalize the variables that deviated from the normal distribution, a logarithmic transformation was performed.

Multiple linear regression analyses were used to examine the association between neuromotor functions and neurotoxicants, after controlling for potential confounders. Pearson correlations were performed to select among the potential confounding variables those to be included in regression analyses. All possible covariates were entered into the multiple regressions when their association with neuromotor scores was significant at $p \leq 0.10$. The evaluation of upper limb functions (postural tremor, reaction time, alternating movements and pointing movements) was done with both hands. However, for many younger children the handling and grip of the instruments with the non-preferred hand was difficult. Thus, statistical analyses were made only on the performance of the preferred hand.

3.5.1. Neurotoxicants selected in the analyses

Several arguments support the use of PCB congener 153 as a marker of exposure to the environmental PCB mixture in the Arctic [34]. First, PCB congener 153 was the most prevalent congener, representing 31.3% and 34.3% of total PCB mixture in cord and child plasma samples, respectively. Second, PCB 153 was highly associated with all other PCB congeners (median correlations were 0.88 and 0.94 for cord and child samples, respectively) and with chlorinated pesticides (from 0.62 to 0.88 for cord plasma and from 0.87 to 0.96 for child plasma samples). PCB 118 was the single dioxin-like congener well detected and was kept for analyses. Although the chlorinated pesticides assessed here were highly associated with PCB 153, we

Table 3a
Descriptive statistics for PCB congeners[a], chlorinated pesticides[a], Hg and Pb concentrations assessed in umbilical cord samples (N=109)

	% Detected	Arith mean[b]	Geo mean[c]	SD	Range	% Total PCB mixture	Pearson r with PCB congener 153
Polychlorinated biphenyls (μg/kg)							
Congener 28	0.9						
Congener 52	51.8						
Congener 99	95.5	26.5	21.1	19.4	4.2–132.8	6.7	0.92** [d]
Congener 101	50.0						
Congener 105	35.5						
Congener 118	91.8	22.8	18.0	16.4	3.6–92.9	5.8	0.84**
Congener 128	0.9						
Congener 138	100	81.4	66.4	57.3	15.2–385.6	20.6	0.98**
Congener 153	100	123.6	99.6	95.2	21.6–652.6	31.3	
Congener 156	49.1						
Congener 170	82.7	18.3	13.9	15.4	4.2–87.1	4.6	0.92**
Congener 180	100	49.1	39.0	37.6	7.4–202.4	12.4	0.95**
Congener 183	50.0						
Congener 187	97.3	23.7	20.1	14.0	4.5–78.5	6.0	0.95**
$\sum$ 14 congeners[e]		394.9	330.3	267.6	99.5–1725.7		0.96**
Chlorinated Pesticides (μg/kg)							
Aldrin	4.5						
β-HCH	39.1						
p,p′ -DDE	100	466.5	371.9	337.0	88.7–2239.1		0.88**
p,p′ -DDT	71.8	20.8	16.2	15.3	4.5–80.0		0.62**
Mirex	29.1						
Hexachlorobenzene	100	68.7	55.7	46.2	12.0–227.9		0.79**
α-Chlordane	0.9						
γ-Chlordane	0						
Cis-Nonachlor	75.5	15.3	11.7	12.3	3.0–63.0		0.74*
Trans-Nonachlor	100	69.7	53.3	54.7	9.8–260.7		0.88*
Oxychlordane	95.5	41.7	29.4	39.0	3.2–250.4		0.88*
Mercury (μg/l)	100	22.2[f]	15.9	18.4	1.8–104.0		0.47**
Lead (μg/dl)	98.2	5.0[g]	4.1	3.7	0.8–27.1		0.23*

Abbreviations: β-HCH, β-hexachlorocyclohexane; *p,p′*-DDE, dichlorodiphenyl dichloroethylene; *p,p′*-DDT, dichlorodiphenyl trichloroethane.

[a] Descriptive statistics are presented for PCB congeners and chlorinated pesticides detected in at least 70% of cord plasma samples.

[b] Arithmetic mean.

[c] Geometric mean.

[d] *$p \leq 0.05$ **$p \leq 0.01$.

[e] Sum of all 14 PCB congeners.

[f] 110.4 nmol/l.

[g] 0.24 (μmol/l).

selected the following ones for subsequent analyses since they were detected in 100% of cord and child plasma samples: *p,p′* -DDE, hexachlorobenzene and *Trans*-Nonachlor. Statistical analyses were performed using blood Hg concentrations to document Hg exposure at testing time since child blood and hair Hg concentrations were highly correlated (r=0.91). Pb concentrations in cord and child blood were also included in analyses. Detailed OC and metal exposures, both prenatal and at testing time, are presented in Tables 3a and 3b, respectively.

3.5.2. Primary analyses

The first analyses examined the association between prenatal neurotoxicants and neuromotor functions. A hierarchical technique was used in the regression analyses with covariates included on the first iteration, followed by cord blood concentrations of the neurotoxicants (PCBs, chlorinated pesticides, Hg, Pb). Prenatal selenium and n3-PUFA were included in the last step when significantly correlated with neuromotor scores ($p \leq 0.10$). Only significant prenatal neurotoxicants were kept for the secondary analyses.

3.5.3. Secondary analyses

Again, hierarchical regressions were used with covariates included in the first step, followed by significant prenatal neurotoxicants, prenatal selenium and n3-PUFA when significant (obtained in the primary analyses), followed by the three postnatal neurotoxicants. Postnatal selenium and n3-PUFA were included in the fifth and last step. When a postnatal neurotoxicant was significantly associated with an outcome, the corresponding prenatal neurotoxicant was

Table 3b
Descriptive statistics for PCB congeners[a], chlorinated pesticides[a], Hg and Pb concentrations assessed in blood or hair samples collected at time of child testing (N=109)

	% Detected	Arith mean[b]	Geo mean[c]	SD	Range	% Total PCB mixture	Pearson r with PCB congener 153
Polychlorinated biphenyls (μg/kg)							
Congener 28	14.5						
Congener 52	48.2						
Congener 99	98.2	30.4	18.8	34.7	2.2–211.5	6.5	0.95** (109)[d]
Congener 101	64.5						
Congener 105	40.9						
Congener 118	95.5	23.7	15.6	23.0	1.8–130.1	5.1	0.91** (109)
Congener 128	5.5						
Congener 138	100	94.0	53.9	112.0	7.4–588.9	20.1	0.99** (109)
Congener 153	100	160.5	84.3	214.1	7.5–1467.2	34.3	
Congener 156	76.4	11.6	7.0	14.3	1.5–81.7	2.5	0.91** (109)
Congener 170	79.1	23.8	11.2	34.4	1.3–207.1	5.1	0.98** (109)
Congener 180	100	64.3	30.8	89.8	2.5–522.4	13.7	0.98** (109)
Congener 183	68.2						
Congener 187	98.2	29.7	17.4	33.0	1.5–153.9	6.3	0.97** (109)
$\sum$ 14 congeners[e]		468.3	271.4	567.6	44.5–3392.9		0.98** (107)
Chlorinated Pesticides (μg/kg)							
Aldrin	4.5						
β-HCH	61.8						
p,p′ -DDE	100	496.9	286.7	581.9	37.9–3081.0		0.96** (109)
p,p′ -DDT	69.1						
Mirex	48.2						
Hexachlorobenzene	100	63.0	46.9	52.7	9.9–275.6		0.91** (109)
α-Chlordane	0.9						
γ-Chlordane	4.5						
Cis-Nonachlor	80.9	18.2	10.7	18.7	1.9–44.3		0.87** (109)
Trans-Nonachlor	100	99.9	55.9	116.1	4.1–706.3		0.93** (109)
Oxychlordane	100	76.8	39.5	105.3	2.9–623.4		0.96** (109)
Blood mercury (μg/l)	100	9.6[f]	5.9	8.9	0.2–38.2		0.37** (109)
Hair mercury (μg/g)	97.3	2.7	1.7	2.6	0.1–13.9		0.36** (109)
Lead (μg/dl)	100	5.4[g]	4.1	5.0	1.0–37.1		0.04 (109)

Abbreviations: β-HCH, β-hexachlorocyclohexane; *p,p′*-DDE, dichlorodiphenyl dichloroethylene; *p,p′*-DDT, dichlorodiphenyl trichloroethane.

[a] Descriptive statistics are presented for PCB congeners and chlorinated pesticides detected in at least 70% of child plasma samples.

[b] Arithmetic mean.

[c] Geometric mean.

[d] N's are provided in parenthesis and *$p \leq 0.05$ **$p \leq 0.01$.

[e] Sum of all 14 PCB congeners.

[f] 47.8 nmol/l.

[g] 0.26 μmol/l.

always included in the model. We then removed from the final models all non significant variables. Since cord blood concentration of Hg, PCBs, chlorinated pesticides and Pb did not reach statistical significance, they are absent from the final models.

4. Results

Among the 110 participants, the main cause of exclusion was a lack of cooperation (n=5 for reaction time, n=7 for pointing and alternating movements, n=10 for sway oscillations), and also for poor comprehension of instructions (n=3 for pointing movements; n=2 for reaction time), or computer problems (n=2 for alternating and pointing movements, n=1 for reaction time; n=5 for sway oscillations). Lack of cooperation was more frequent in younger children, especially in sway conditions. *T*-tests were performed to compare PCB, Hg and Pb blood concentrations between participants and children excluded from statistical analyses (for lack of cooperation or poor comprehension of the task). Results revealed no significant differences between groups on all prenatal and postnatal neurotoxicants.

4.1. Prenatal exposure and exposure at testing time

Descriptive statistics of PCB congeners, chlorinated pesticide, Hg and Pb concentrations obtained in blood and hair samples are presented in Tables 3a and 3b. Correlations between environmental contaminants are presented in Table 4. Selenium concentrations averaged 4.4 μmol/l in cord blood (SD=2.1, n=56) and 5.2 μmol/l in child blood (SD=4.9, n=110). Docosahexaenoic acid (DHA) averaged 3.4% of total phospholipids in cord plasma (SD=1.1, n=101) and 2.4% in child plasma at testing time (SD=1.0, n=109) while eicosapentaenoic acid (EPA) averaged 0.4% of total phospholipids in cord plasma (SD=0.4, n=101) and 0.5% in child plasma at testing time (SD=0.6, n=109).

4.2. Potential covariates

The following covariates, associated at $p \leq 0.10$ with the outcomes, were included in statistical analyses: for *reaction time*—child age, duration of breastfeeding, HOME inventory, mother's education, head circumference, height, weight, consumption of alcohol and marijuana during the pregnancy; for *alternating movements*—child age, HOME inventory, height, weight, head circumference, use of alcohol and marijuana during pregnancy, mother's age, child selenium, child EPA and DHA; for *pointing movements*—mother's education, weight, HOME inventory, child EPA and child DHA; for *postural sway*—consumption of marijuana during pregnancy, duration of breastfeeding, mother's education and child DHA. Moreover, in the absence of data on feet surface area, we controlled for other growth parameters in regression models for postural sway (weight, height, body mass index (kg/m^2), head circumference). In Table 5, only significant covariates were included in the models.

4.3. Neurological and motor development

Gross motor development and neurological examination were unaffected by prenatal and postnatal PCB, chlorinated pesticides, Hg and Pb exposures. However, fine neuromotor functions were associated mostly with blood Pb concentrations at testing time. As shown in Table 5, while controlling for covariates, higher Pb concentrations at testing time were significantly associated with increased reaction time, which meant that the child was slower to respond. Fig. 1a represents partial regression plot of blood Pb concentration at testing time by reaction time.

In the static conditions, blood Pb concentrations at testing time were significantly associated with a larger

Table 4
Intercorrelations between environmental contaminants

	PCB 153		Mercury			Lead	
	Cord	Child	Cord	Child blood	Child hair	Cord	Child
PCB 153							
Cord		0.41**(108)	0.47**(109)	0.36**(109)	0.38**(109)	0.23*(109)	0.09(109)
Child			0.40**(109)	0.37**(109)	0.36**(109)	0.14(109)	0.04(109)
Mercury							
Cord				0.43**(110)	0.45**(110)	0.34**(110)	−0.01(110)
Child blood					0.91**(110)	0.11(110)	0.36**(110)
Child hair						0.06(110)	0.19*(110)
Lead							
Cord							0.23*(110)
Child							

* $p \leq 0.05$; N's are in parenthesis.
** $p \leq 0.001$; N's are in parenthesis.

Table 5
Linear regression analyses for neuromotor variables

Characteristics	*N*	Predictors	Pearson *r*	Stand. B	*F*	R^2
Reaction time	93	Child age	−0.29**	−0.27**		
		HOME	−0.30***	−0.35***		
		Mother's education	0.20*	0.26**		
		Breastfeeding duration	0.23*	0.21*		
		Head circumference	−0.21*	−0.23*		
		Child Pb	0.21*	0.24**	8.89***	0.38
Sway (static)						
Velocity	96	Child Pb	0.24**	0.24*	5.75*	0.06
Sagittal	97	Child Pb	0.22*	0.22*	4.90*	0.05
Sway (balance)						
Tandem (sagittal sway)	88	Weight	0.19*	0.22*		
		Mother's education	−0.17^{+}	0.24*		
		Child Pb	0.19*	−0.18^{+}	3.77*	0.12
Tandem (transversal sway)	87	Weight	0.18*	0.27*		
		Child PCB 153	0.15^{+}	0.22*		
		Child Pb	0.22*	0.26*	4.41**	0.14
Alternating movements						
Coefficient of variation	99	Alcohol during pregnancy	0.21*	0.19^{+}		
		Child Pb	0.24**	0.22*	4.99**	0.09
Coherence between hands	105	Child Pb	−0.29***	−0.29**	9.65**	0.09
Synkinesis	104	Head circumference	−0.18*	−0.18^{+}		
		Mother's age	0.21*	0.18^{+} *		
		Child Pb	0.24**	0.23*	4.80**	0.13
Pointing movements						
Tremor	99	Child Hg	0.29**	0.20*	7.61***	0.14
		Child Pb	0.32***	0.24*		

* $p \leq 0.05$.
** $p \leq 0.01$.
*** $p \leq 0.001$.
$^{+}$ $p \leq 0.10$.

sagittal sway and a higher sway velocity (Table 5 and Fig. 1b) but not with transverse oscillations (not illustrated). In balance conditions, blood Pb concentrations at testing time were significantly associated with larger sagittal and transversal sway oscillations in tandem position (heel to toes). Child weight was the principal covariate in these conditions (heavier children had larger sway oscillations). A Pearson correlation of 0.40 ($p \leq .01$) was observed between sagittal and transversal sway in the tandem condition. Velocity and sagittal sway were also associated (r=0.60, $p \leq 0.01$). Blood PCB 153 concentration at testing time was associated with transversal sway in balance conditions. This association was not observed when PCB 118, *p,p′* -DDE, hexachlorobenzene or *Trans*-Nonachlor was include in multiple regression

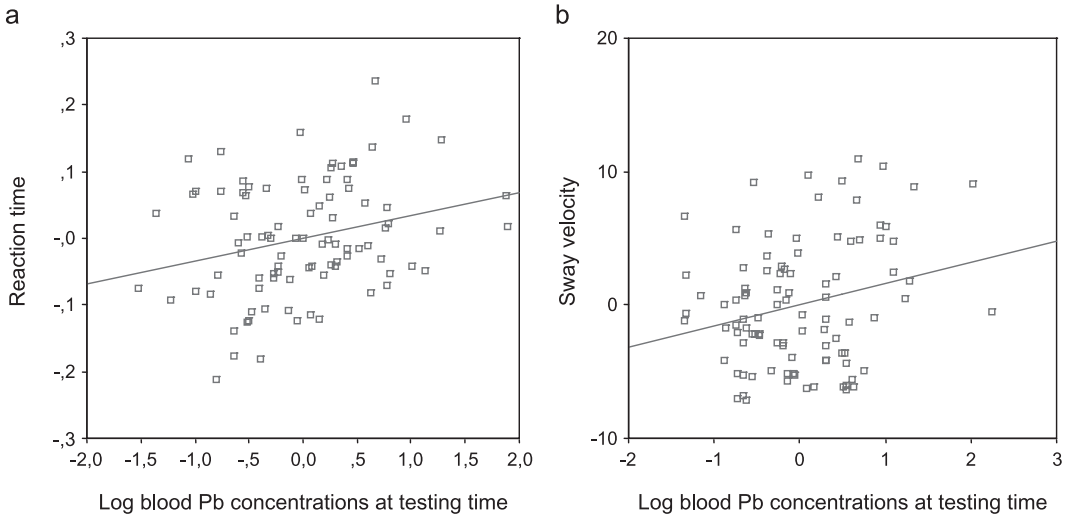

Fig. 1. Partial plots for reaction time and sway velocity.

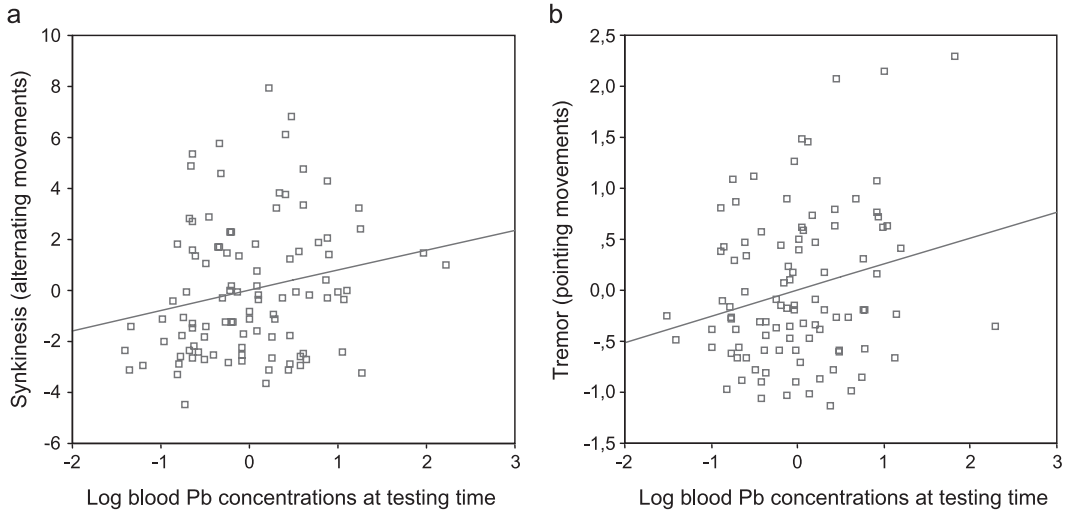

Fig. 2. Partial plots for alternating movements (synkinesis) and pointing movements (tremor).

instead of PCB 153. Blood concentrations of PCBs, chlorinated pesticides, Hg and Pb were not related to one foot balance condition.

Blood Pb concentrations were related to alterations in the morphology of alternating movements (Table 5) but not to movement velocity (not illustrated). Pb concentrations at testing time were associated with more movement irregularity (coefficient of variation), less coherence between hands and increased contralateral mirror movements (synkinesis, see Fig. 2a) during unilateral movements. The 3 dimensions assessed (coefficient of variation, coherence between hands and synkinesis) were not significantly intercorrelated (Pearson r varied between 0.04 and 0.12, p=ns).

Regarding pointing movements, Blood Pb and Hg concentrations at testing were significantly associated with higher action tremor amplitude when the child touched the targets (Table 5 and Fig. 2b). The other dependent variables studied for pointing movements (irregularity, contact duration) were not associated with environmental contaminants. Hg, Pb, PCBs and pesticides concentrations, whether assessed in cord or blood samples at testing time, were not associated with postural tremor (using accelerometer).

Pb exposure can produce anemia [31] and iron deficiency can interfere with normal development of children. Because iron deficiency could be an important confounding variable, we also controlled the hemoglobin level in our regression models. No significant differences were found after controlling for this variable. In fact, in our cohort, hemoglobin levels were not significantly linked to either blood Pb level or with dependent variables.

5. Discussion

In this cohort of preschool aged children, we did not find any adverse effects of prenatal exposure to PCBs, pesticides and Hg on the neurological status, gross motor functions or pre-clinical motor signs assessed (tremor, sway oscillations, reaction time, alternating and pointing movements) at the observed levels of exposure. We observed significant associations between blood Pb concentrations at testing time and pre-clinical alterations of neuromotor functions (reaction time, alternating movements, pointing movements, sway oscillations). These associations persisted after controlling for confounding variables, and were not attributed to prenatal Pb exposure. Moreover, beneficial effects of n3-PUFA and selenium were not observed.

In a group of 7- to 12-year old children born to PCB poisoned Taiwanese mothers, Chen and Hsu [11] did not report anomalies with the standard neurological examination, but soft neurological signs such as mirror movements, poor finger-thumb opposition and choreiform movements were observed with increased PCB exposure. In our cohort, finger-thumb opposition was not assessed but mirror movements were measured in alternating movements, and choreiform movements would have been detected with tremor tests. We did not find any such adverse effects with prenatal exposure to PCBs and chlorinated pesticides. Taiwanese children were exposed to much higher PCB concentrations than what is observed in our cohort. The only significant association with exposure to OCs was observed with blood PCB 153 concentrations at testing time and larger transversal sway oscillations in balance condition. Two factors may indicate that this association is likely to be spurious. First, PCB 118, p,p'-DDE, hexachlorobenzene and *Trans*-Nonachlor were not related to this outcome despite that these OCs were strongly correlated with PCB 153. Secondly, similar to past studies, there is no clear pattern of motor effects with OC exposure.

With regard to adverse effects of prenatal Hg exposure on motor function, cord blood Hg concentrations were not associated to the documented outcomes. In the study conducted in French Guiana, Cordier et al. [13] did not

find major neurological signs in the children examined but they observed an increase in deep tendon reflexes associated with maternal hair Hg levels, as it was previously reported for boys in the Canadian Cree Indian population [33]. However, hair Hg concentrations observed in those studies were noticeably higher than the hair Hg levels observed in our study. This could explain the discrepancy between the results even though we used the same neurological examination as used by Cordier et al. [13]. Moreover, our results do not corroborate the association observed between cord blood Hg concentrations and reaction time reported by Grandjean in the Faroese cohort of 7-year-old children [22]. However, the testing procedures used in both studies are very different and are likely to explain this discrepancy. Children from our cohort were asked to press a button each time an auditory stimulus was presented, while Faroese children were asked to press a button each time a cat was seen among a series of animal silhouettes flashed on a computer screen. In the later task, the additional animals cause visual distraction. The child must engage in discrimination of stimuli thus increasing the complexity of the task. Faroese protocol is likely to involve more complex selective attention functions and more complex mental processing than the testing procedures used in the present study. Finally, higher action tremor amplitude during pointing movements was significantly correlated with blood Hg concentration at time of testing. A similar Hg effect was observed among adults exposed to Hg when action tremor was assessed with the same testing protocol [4].

Many of the Pb effects observed in this cohort are similar to those reported in past studies. Like in other cohorts, Pb exposure during childhood was associated with increased reaction time in school age children [23,26]. Reaction time has also been linked to Pb exposure in more complex attention tasks [48]. However, these results were obtained at higher blood Pb levels than those observed in the present study. With a computerized force platform designed to assess subtle variation of sway, we were able to detect unsteadiness in static and balance conditions with increased blood Pb concentrations at testing time. Balance items that depend on the examiner's observations are likely to be less sensitive to subtle sway variations than when assessed using a force platform. Our results are consistent with two reports based on the Cincinnati cohort indicating that blood Pb levels during childhood were associated with reduced balance when postural sway was assessed with a microprocessor-based force platform [6,7]. In our study, Pb exposure during childhood was associated with more irregularity, more mirror movements and less coherence between hands in alternating movements. These results on upper limb function are consistent with findings from Dietrich et al. [18], using Bruininks Oseretsky Test of Motor Proficiency battery (BOTMP [8]). They observed a significant association between postnatal blood Pb levels and poorer scores on measures of bilateral coordination, upper limb speed and dexterity, and fine motor skills in 6-year-old children. Using the same battery (BOTMP), Wasserman et al. [47] also reported that Pb exposure during childhood was associated with poorer fine motor function. Hand tremor has not been frequently explored in children exposed to environmental contaminants but action tremor during pointing movements was significantly correlated with blood Pb levels at testing time in our cohort.

In this study, the average blood Pb concentrations at testing time (4.1 μg/dl) was twice as high as that found in the general population of Southern Quebec but was about 1.5 times lower than those observed in 5-year-old children from Boston (6.4 μg/dl) [3], 2–3 times lower than those observed in 6-year-old children from Cincinnati (10.1 μg/dl) [18] and in 7-year-old children from Port Pirie (11.6 μg/dl) [2]. After repeated downward revisions, the intervention level of Pb was set at blood concentrations of 10 μg/dl (0.48 μmol/l) by the Center for Disease Control [44]. In our cohort, 11 children (10%) had a blood Pb level = 10 μg/dl. We performed the regression analyses without these 11 children and results remained significant for the following outcomes: reaction time, sagittal sway in tandem condition and synkinesis in alternating movements. Moreover, two participants had the very high (>4 standard deviations) blood Pb levels of 37.09 and 30.46 μg/dl. We performed the regression analyses without them and the results were similar to the previous ones except for one: the association between blood Pb at testing time and the coefficient of variation in alternating movements was no longer significant.

Various Pb effects were observed at concentrations lower than 10 μg/dl, including adverse effects on electrophysiology, neurochemistry, behavior, cognitive functions and school performance [10,30]. Negative consequences of Pb exposure below 5.0 μg/dl have been noted in IQ, attention, visual-motor integration, academic skills including arithmetic and reading scores [30]. Moreover, in a recent publication, Chiodo et al. [12] reported associations between neurobehavioral deficits and Pb levels as low as 3 μg/dl. Our results extend these observations by showing that specific neuromotor functions are also affected at low-level lead exposure during childhood. These results suggest that reaction time, fine motor coordination and balance should be added to the neuromotor signature of lead exposure.

One may argue that the clinical significance of the neuromotor alterations observed in this cohort of preschool aged children depends on whether they predict later motor development or school functioning. It is likely that fine neuromotor deficits interfere with different skills, for example, with the acquisition of writing skills. Also, it remains to be determined whether the subtle motor changes observed here persist as the child gets older. Some reports suggest that adverse effects of Pb exposure during childhood are only partially reversed by a subsequent decline in blood Pb level [43].

Several features in our study design may have enabled us to find significant results despite the relatively small sample size. First, the study sample was somewhat homogeneous with regard to age, culture, education and nutrition. Children were also free of confounding medical factors. Second, an effort was made to select quantitative neuromotor tests more sensitive than the traditional motor subscales in neurobehavioral test batteries to measure pre-clinical alterations in motor functions [4,5]. Even though the selected instruments were successfully adapted for children of preschool age, cooperation was the main cause of exclusion, especially affecting sway measures. For all dependant variables, there was no significant difference between included subjects and those that were eliminated for lack of cooperation with regards to cord and child blood levels of environmental contaminants. However, for postural sway oscillations, eliminated subjects tended to have higher blood Pb concentrations at testing time (t=−2.17, p=0.06). It is possible that this lack of cooperation is an effect of Pb exposure.

6. Conclusions

In summary, in this study, environmental contaminants (Hg, Pb, PCBs and pesticides) were examined in relation to neuromotor, gross motor and neurological functions among preschool Inuit children exposed through consumption of traditional foods. A broad range of potential confounders was examined. No adverse effects were observed on either gross motor function or neurological status. However, we found that a small elevation in blood Pb levels during childhood was associated with decreased performance on several dimensions of neuromotor function. Higher blood Pb concentrations at preschool age was associated with slower reaction time, larger sway oscillations, as well as poorer alternating movements (less coherence between hands, increased mirror movements and irregularity) and increased action tremor during pointing movements. For some of these outcomes, neuromotor effects of Pb exposure were observed at blood concentrations below 10 μg/dl. Moreover, negative effects of Hg concentrations at testing time were observed on action tremor during pointing movements. Larger transversal sway in tandem condition was associated with blood PCB 153 concentrations at testing time. Longitudinal follow-up of our cohort would help determine if the neuromotor deficits observed will persist through childhood and if they are related to school performance. These results underline the interest of using quantitative measures designed to quantify sub-clinical changes in neurobehavioral teratology.

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