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Mercury concentrations in historic autopsies from Grassy Narrows First Nation

J.L. Lee [a,c], M. Fraser [b], A. Philibert [c], D. Saint-Amour [d], D. Mergler [c,*], M. Fillion [c,e]

[a] Université TÉLUQ, Département Science et Technologie, Montréal, QC, Canada
[b] École de technologie supérieure, Department of General Education, Montreal, QC, Canada
[c] Université du Québec à Montréal, Centre de recherche interdisciplinaire sur le bien-être, la santé, la société et l'environnement (Cinbiose), Montréal, QC, Canada
[d] Université du Québec à Montréal, Department of Psychology, Montréal, QC, Canada
[e] Département Science et Technologie, Université TÉLUQ, Montréal, QC, Canada

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ABSTRACT

The Asubpeeschoseewagong Anishinabek (Grassy Narrows First Nation) have been engaged in a decades-long struggle to improve their health and environment after an industrial discharge of between 9000 and 11,000 kg of mercury (Hg) into their river system. Hg concentrations in freshwater fish, central to their cultural identity, livelihood and diet, were among the highest ever reported. Between 1972 and 1992, a Canadian government program measured Hg concentrations in routine autopsies from this community. In 2017, Grassy Narrows obtained their community's autopsy reports. The present study examined the distribution of total mercury (T-Hg) and inorganic mercury (I-Hg) in brain, organ, blood, and hair samples from 21 historic autopsy reports, spanning 1976 to 1986.

T-Hg median in blood and hair were 6 ppb (range = 2.5–100) and 2.47 ppm (0.41–49.8), respectively. Hg was present in all brain regions (T-Hg median = 53 ppb, 13–299), with highest concentrations in the cerebellum (63 ppb, 16–365) and basal ganglia (58 ppb, 10–420). I-Hg constituted approximately 25 % of T-Hg in all brain regions. In organ samples, T-Hg was higher [renal medulla (290 ppb, 28–4400), renal cortex (1240 ppb, 100–6000), liver (300 ppb, 64–2400)], with greater proportion of I-Hg (82 %, 74 %, 63 %, respectively). Significant correlations were observed between T-Hg in hair and most brain regions ($\rho = 0.70$–0.77), blood ($\rho = 0.56$), and renal cortex ($\rho = 0.61$). While Hg accumulation in the cerebellum has been documented, the basal ganglia has seldom been an object of interest in the Hg scientific literature. The presence of Hg in the brain and other organs complement current studies on the long-term health consequences of Hg in this community. The findings further suggest the need for a closer examination of the role of basal ganglia in Hg-related disorders.

1. Introduction

Between 1962 and 1970, a chloralkali plant operated by the Reed Paper Group in Dryden, Kenora, Ontario, discharged between 9000 and 11,000 kg of inorganic mercury (I-Hg) in the English-Wabigoon River system, which flows into the territorial waters of the Grassy Narrows First Nation [49]. Once in the aquatic system, I-Hg is transformed into methyl mercury (MeHg), which bioaccumulates and biomagnifies in the aquatic food chain, exposing community members to mercury (Hg) through the consumption of fish [30,49,65]. Hg concentrations in freshwater fish were among the highest ever reported, with values as high as 27.8 ppm in northern pike [21] and 24 ppm in walleye [5]. Prior to the discovery of the Hg contamination in 1970, freshwater fish, particularly walleye, was central to the economic livelihood, diet, and cultural traditions of the community [79]. Most families in Grassy Narrows ate fish every day and depended on the river system for their livelihood as fishing guides and commercial fishers [82].

Recent studies at Grassy Narrows have associated past long-term Hg exposure (1970–1997) to premature mortality [59], visual field constriction [60,77], and a range of coexisting symptoms of nervous system dysfunction, including loss of motor control, neurocognitive deficits, sensory impairments, and affective disorders [57,58]. Hg exposure over three generations has also been shown to carry profound intergenerational effects on the mental health of the present-day children and youth of Grassy Narrows, contributing to a prevalence of attempted suicide three times higher than that of other First Nations

* Corresponding author.
E-mail address: mergler.donna@uqam.ca (D. Mergler).

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[46].

The symptoms and lesions associated with mercury poisoning exist on a continuum, depending on the source, duration, and timing of exposure. Minamata disease, as originally documented in Japanese adults exposed to high levels of MeHg from Minamata Bay, is associated with visual field constriction, ataxia and dysarthria, hearing loss and disequilibrium, tremor, cognitive impairment and psychiatric features [32]. Congenital mercury poisoning resembles cerebral palsy, with symptoms such as intellectual disability, dysarthria, ataxia, gait disorders, involuntary movements, pathological reflex, strabismus, and hypersalivation. Functional losses accelerate with age [88]. Neuroimaging studies of Minamata disease patients show a significant reduction in grey matter in the cerebellum and calcarine cortex in both adults and children, and in the thalamus of fetal-type cases [31], as well as atrophy in the postcentral gyrus [35]. Studies carried out between 1975 and 2011 in Grassy Narrows reported a high prevalence of persons with signs and symptoms consistent with Hg poisoning, with many matching the diagnostic criteria for Minamata disease [27,71].

MeHg from fish consumption is rapidly absorbed into the bloodstream and distributed to tissues throughout the body [10,56], and crosses the blood-brain barrier through active amino acid transporters [8,12,13,17] (see Fig. 1 for a graphical summary of the metabolism of MeHg from fish consumption). A fraction of MeHg in the blood is taken up into scalp hair, making it a small but not insignificant route of elimination [12]. MeHg is gradually demethylated into I-Hg in the brain

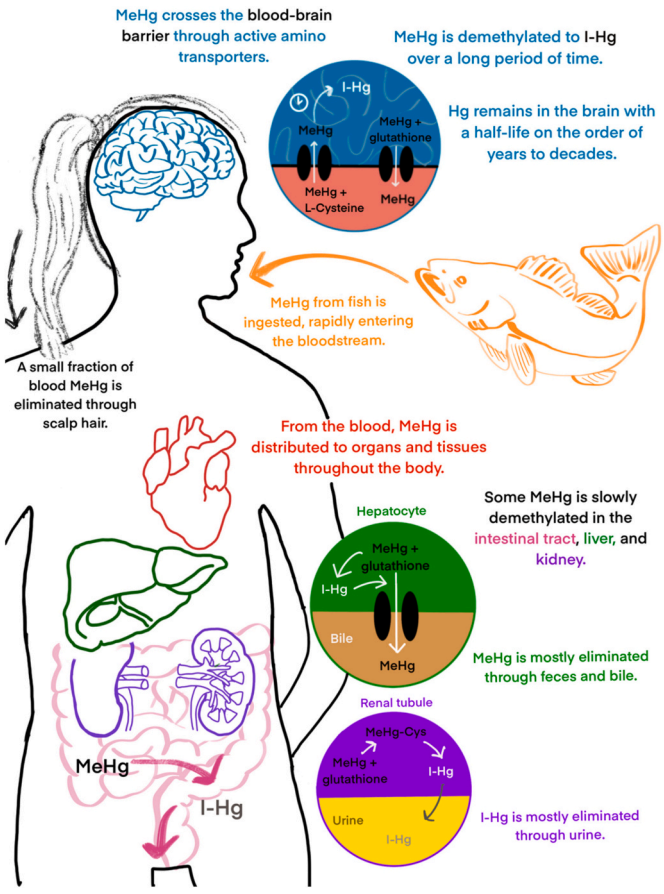

Fig. 1. The metabolism of MeHg consumed through fish. Ingested MeHg crosses the blood-brain barrier through active amino acid transporters. It is slowly demethylated into I-Hg in the brain, where it remains with a half-life on the order of years to decades. Demethylation also occurs in the intestinal tract, liver, and kidney. MeHg is gradually excreted through scalp hair, bile, and feces, while I-Hg is mostly eliminated through urine after demethylation in the kidney.

[14,22,81], as well as in the intestinal tract [64], liver, and kidney [61], then excreted through feces and urine over a long period of time [2,12,55,80].

Much of what is currently known about Hg deposition in the brain and other organs comes from the autopsy findings of individuals from communities around the world who have experienced exposure to MeHg through freshwater fish or marine fish and animal consumption [23,50,51,53]. Fetal and childhood exposure is thought to lead to a more diffuse pattern of MeHg throughout the brain, while adult exposure is more localized. [19]. Across case studies spanning about 50 years, the cerebellum has been identified as an area of particular interest, often containing higher T-Hg compared to other brain regions, in both adults [53] and infants [36].

While the neurotoxic effects of lifetime Hg exposure are manifest in this community, the distribution of Hg in the whole brain, brain regions and organs of deceased individuals from Grassy Narrows has not yet been characterized. The objectives of the present study were (1) to characterize the distribution of total (T-Hg) and inorganic Hg (I-Hg) in the brain and other organs from historic autopsies of persons from Grassy Narrows First Nation, and (2) to examine their association with blood and hair Hg at time of death.

2. Methods

This project is part of an ongoing community-university research partnership between Grassy Narrows First Nation and university-based researchers in accordance with OCAP® principles of Ownership, Control, Access, and Possession of First Nations information, a registered trademark of the First Nations Information Governance Centre [75].

Autopsies are routinely performed for suspicious, unusual, or unnatural deaths. Between 1972 and 1992, samples from some routine autopsies, performed by the coroner's office in Kenora, Ontario, were analyzed for mercury. These reports, which included mercury measurements in brain tissue, blood, hair, and major organs, were archived at the First Nations and Inuit Health Branch of Health Canada (now Indigenous Services Canada) and the Ontario Ministry of Health and Long-Term Care. In 2017, Grassy Narrows First Nations leadership obtained all fifty-three of their community's autopsy reports and shared them with the research team.

2.1. Autopsy reports

For the present study, the following inclusion criteria were applied to the 53 autopsy reports: (i) the individual was at least 10 years old at time of death; (ii) the report included at least one total Hg (T-Hg) and one inorganic Hg (I-Hg) measurement in the brain; (iii) the report included a blood T-Hg measurement taken at time of death. A total of 21 reports, from autopsies conducted between 1976 and 1986, were retained for analyses. These autopsy reports also included Hg measurements from the renal cortex ($n = 20$), renal medulla ($n = 17$), liver ($n = 20$), heart ($n = 9$), and first centimeter of hair ($n = 19$).

Over the 10-year period during which the autopsy reports were produced, brain tissue sampling methods were not consistent. Some reports included Hg measurements identified as "brain" without mentioning a specific region, while other reports included Hg measurements from separate brain regions– some from the upper and/or lower region of a particular structure, others from the right and/or left hemispheres. Measurements were labeled with different levels of specificity (e.g., "thalamus" vs. "lateral geniculate body"). To overcome these methodological inconsistencies, and to allow for comparisons across major brain regions, Hg measurements were grouped based on anatomical region, as detailed in the tree structure shown in Fig. 2. First, T-Hg concentrations from the right and left hemispheres of the same brain region or subregion were averaged. Second, where appropriate, T-Hg concentrations from specific brain sub-regions (Fig. 2, yellow boxes) were averaged to constitute a higher-level "major brain region" (Fig. 2,

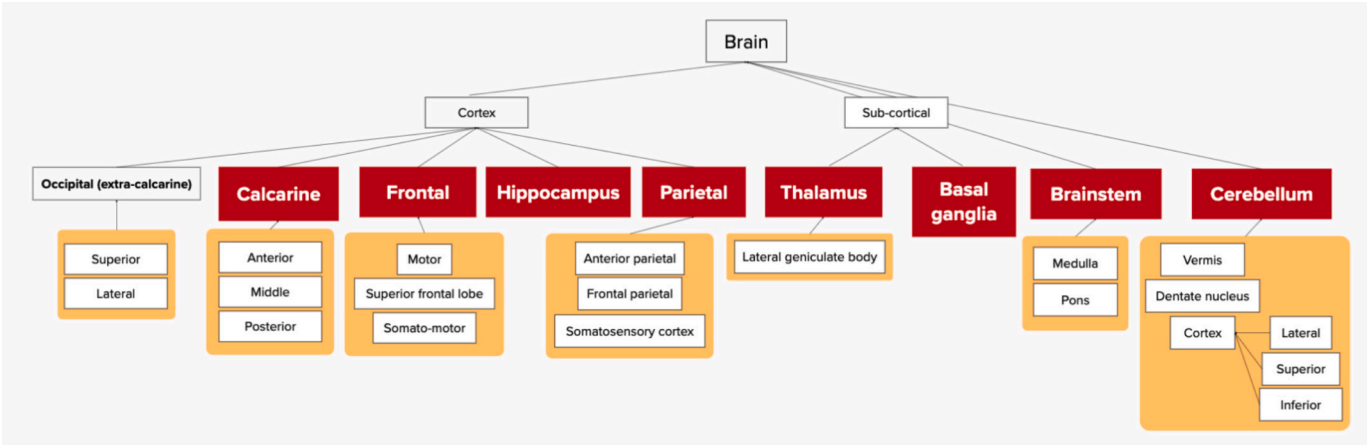

Fig. 2. Brain region tree structure. Hg measurements from each brain subregion (yellow) were grouped into their corresponding major brain region (red) and were averaged along with measurements taken from unspecified locations of that region to produce an overall estimate of the Hg concentration in the major brain region. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

red boxes). In the autopsy reports, brain tissue samples were sorted and averaged into the following eight major brain regions: calcarine cortex, parietal lobe, frontal lobe, medulla, pons, hippocampus, thalamus, basal ganglia, and cerebellum.

For intra-brain comparisons, only individuals (n = 11) whose autopsy reports contained measurements for all eight major brain regions were used. Whole brain T-Hg was calculated by averaging the T-Hg values for available brain regions.

Information concerning the method of Hg analysis was sparse and rarely included in the autopsy reports obtained. An archived government document from the Ontario Ministry of Labour indicates that, for at least some of the autopsy reports corresponding to a subset of individuals who died in 1976, samples were analyzed by the Magos cold vapour atomic absorption method [39,42] by the Radiation Protection Laboratory of the Ontario Ministry of Labour to determine T-Hg and I-Hg [67]. Some analyses were done by the Trace Contaminant Laboratory of the Ontario Ministry of the Environment, where T-Hg was determined by a hot block digestion method [6] and where MeHg was determined through a modified version of Westöö's technique [6,83]. The report states that postmortem examinations were typically conducted within 48 h of death, though in some cases, examinations were performed up to one week later. Brain samples were fixed in mercury-free buffered formaldehyde in glass jars, except for rare cases in which the brain was transported in cooled containers and analyzed in a fresh rather than fixed state [67]. The mercury content of some samples was confirmed in the laboratory of Dr. Thomas Clarkson in Rochester, New York [11]. Concentrations are expressed as ppb wet weight.

2.2. Statistical analyses

Given the small sample size (n = 21) and the non-unimodal distribution of data, a series of non-parametric analyses was conducted. Non-adjusted correlations between continuous variables were assessed using Spearman's rho (ρ). A series of non-parametric match-paired analyses (Wilcoxon Signed Rank with S approximation) was performed for intra-brain comparisons of T-Hg concentrations for those individuals for which data were available for all eight major brain regions (n = 11). The Mann-Whitney U test was performed to test differences by gender in blood T-Hg concentration.

The level of statistical significance was set at $p < 0.05$.

JMP® Pro 16 (SAS, 2021) was used for database creation and management. Statistical analyses were performed using JMP® Pro 16 (SAS, 2021) and Python 3.7.6 (2020). Data visualizations were produced using Python 3.7.6 (2020) using *matplotlib* and *seaborn* packages.

3. Results

The 21 autopsies included 10 women, whose ages at death ranged from 25 to 72 y (median: 53 y), and 11 men (age at death: 16–72 y; median: 24 y). All were performed between 1976 and 1986. Fig. 3 shows the distribution of sex and lifespan for each of the 21 individuals.

Table 1 presents T-Hg, I-Hg, and the organic fraction in blood, hair, brain regions and organs, while Supplementary Fig. 1a and 1b provide graphic representations of T-Hg and I-Hg in brain regions and organs.

Blood and hair Hg, measured at the time of autopsy, showed a median of 6.0 μg/L (n = 21) and 2.47 μg/g (n = 19), respectively (Table 1). There was no significant difference in blood T-Hg between women (median = 8.0 μg/L, n = 10) and men (median = 5.0 μg/L, n = 11) (Mann-Whitney U = 34.0; p = 0.07 two-tailed). For the 10 (out of 21) blood samples for which I-Hg was measured, the median percentage of I-Hg relative to T-Hg was 39.9 % (IQR: 25 % - 76 %). No relation was

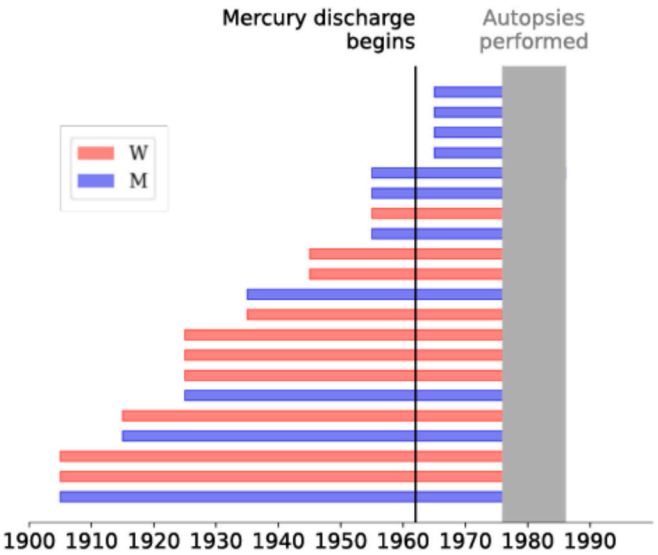

Fig. 3. Individual lifespan and sex distributions of autopsies performed between 1976 and 1986. Each horizontal bar represents the lifespan of an individual (from date of birth to autopsy period), ordered vertically according to year of birth (n = 21). The black vertical line indicates the beginning of Hg discharge into Grassy Narrows' territorial waters. Red lines represent women and blue lines represent men. Year of birth is rounded to the nearest mid-decade to preserve anonymity. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
Average total and inorganic mercury concentrations in blood, hair, brain regions, kidney, liver and heart.

	Total Hg concentration (ppb)						Inorganic Hg concentration (ppb)						Organic fraction (% MeHg of T-Hg)					
	n	Min	25th	Median	75 th	Max	*N*	Min	25 th	Median	75 th	Max	*n*	Min	25 th	Median	75 th	Max
Blood (μg/L)	21	2.5	2.5	6.0	12.0	100	10	1.5	2.0	2.2	12.5	62	10	0.0	24.5	60.1	75.0	84.6
Hair (first cm, ppm)	19	0.41	1.50	2.47	6.10	49.8	–	–	–	–	–	–	–	–	–	–	–	–
Frontal	15	12	26	43	91	270	15	2	7	9	39	82	15	1.7	71.9	75.2	78.5	82.8
Parietal	13	6	18	43	63	310	13	2	6	11	49	67	13	0.0	66.7	75.0	77.9	87.5
Calcarine	21	9	29	49	64	323	21	5	8	12	28	199	21	13.3	60.0	72.1	75.5	88.0
Thalamus	14	8	25	57	108	330	14	2	5	14	48	110	14	4.2	50.8	74.7	80.4	93.8
Basal ganglia	14	10	20	58	155	420	14	2	6	14	48	80	14	2.4	70.1	75.4	80.4	86.4
Hippocampus	12	7	36	46	165	290	12	5	8	19	35	150	12	28.6	51.5	72.2	79.4	82.6
Cerebellum	18	16	24	63	122	365	18	2	8	15	31	158	18	36.0	63.0	73.2	79.9	87.2
Brain Stem	16	8	16	51	106	330	16	2	7	11	44	185	16	0.0	55.5	66.1	78.2	82.0
Medulla	13	7	19	54	120	250	13	2	10	14	39	100	13	11.4	50.0	63.5	76.0	83.8
Pons	16	9	16	45	94	410	16	2	5	11	44	270	16	0.0	52.4	74.3	80.1	85.7
Renal medulla	17	28	160	290	600	4400	17	23	85	220	630	2300	17	0.0[a]	8.6	17.9	34.0	75.0
Renal cortex	20	100	595	1155	1835	6000	20	79	428	775	1302	5290	20	0.0	17.9	26.3	33.7	48.3
Liver	20	64	220	300	742	2400	19	32	125	220	460	1500	19	0.0	23.6	37.5	47.1	74.1
Heart	9	20	25	39	120	280	9	8	11	29	62	190	9	0.0	32.1	45.5	50.8	68.0

[a] Organic fraction calculated as 100 % minus inorganic fraction, with negative values adjusted to 0.

observed with age at death for either blood or hair (Spearman rank correlation; $\rho = 0.25$, $p = 0.27$, $n = 21$ and $\rho = 0.22$, $p = 0.37$, $n = 19$, respectively).

Among brain regions, the highest median concentrations of T-Hg were in the cerebellum, basal ganglia, and thalamus (Table 1). No relation was observed between age at death and T-Hg or I-Hg in any major brain region (Spearman $\rho < 0.28$, $p > 0.34$). Across major brain regions, the median proportion of MeHg was between 63.5 % and 75.2 %. The single highest T-Hg measurement taken (420 ppb) was observed in the right basal ganglia of a female in her 50s.

The kidneys presented the highest T-Hg concentrations (Table 1). Wilcoxon signed-rank tests found no differences in Hg levels between men and women for the renal medulla (T-Hg W = 1.7, $p = 0.08$, $n = 17$; I-Hg W = 1.0, $p = 0.30$, $n = 17$), renal cortex (T-Hg W = 1.5, $p = 0.14$, $n = 20$; I-Hg W = 1.5, $p = 0.12$, $n = 20$), and liver (T-Hg W = 1.2, $p = 0.22$, $n = 20$; I-Hg W = 1.31, $p = 0.19$, $n = 19$). No correlation was found between age at death and Hg concentrations in the renal medulla (T-Hg $\rho = -0.26$, $p = 0.31$, $n = 17$; I-Hg $\rho = -0.37$, $p = 0.14$, $n = 17$), renal cortex (T-Hg $\rho = -0.23$, $p = 0.33$, $n = 20$; I-Hg $\rho = -0.26$, $p = 0.27$, $n = 20$), and liver (T-Hg $\rho = -0.20$, $p = 0.41$, $n = 20$; I-Hg $\rho = -0.23$, $p = 0.34$, $n = 19$). The organic fraction was considerably lower in the kidneys, liver, and heart, compared to that in the brain (Table 1). Indeed, I-Hg constituted approximately 80 % of T-Hg in the kidneys (renal medulla median: 82 %; renal cortex median: 74 %), and over half of the T-Hg in the liver and heart (median 62 % and 54 %, respectively).

Match-paired comparisons in T-Hg and I-Hg between brain regions are presented in Table 2 (Wilcoxon signed-rank test). The cerebellum showed significantly higher T-Hg compared to other regions, except for

Table 2
Match-paired comparisons of total and inorganic mercury concentrations between brain regions.

Pair	*n*	Total Hg concentration			Inorganic Hg concentration		
		Mean difference (ppb)[a]	S[b]	*p*	Mean difference (ppb)	S	*p*
Cerebellum(1) - Basal Ganglia(2)	14	6.28	73.5	0.09	7.62	61.5	0.13
Cerebellum – Thalamus	**14**	**22.91**	**84.0**	**0.02**	**6.21**	**83.0**	**0.03**
Cerebellum - Brain Stem	**16**	**19.74**	**126.0**	**<0.01**	−3.37	77.5	0.31
Cerebellum – Calcarine	**18**	**9.03**	**128.5**	**0.03**	−3.47	87.0	0.47
Cerebellum – Hippocampus	12	16.26	54.0	0.12	3.79	50.5	0.18
Cerebellum – Parietal	**13**	**15.76**	**75.5**	**0.02**	2.80	66.0	0.08
Cerebellum – Frontal	**15**	**31.04**	**92.0**	**0.01**	**10.34**	**93.0**	**0.01**
Basal Ganglia – Thalamus	13	17.85	64.0	0.10	−1.67	32.0	0.32
Basal Ganglia - Brain Stem	14	13.71	68.0	0.17	−12.07	39.5	0.66
Basal Ganglia – Calcarine	14	1.20	59.0	0.34	−13.34	36.5	0.84
Basal Ganglia – Hippocampus	12	0.29	44.0	0.35	−8.46	28.0	0.67
Basal Ganglia – Parietal	13	24.38	68.0	0.06	3.63	34.0	0.25
Basal Ganglia – Frontal	**14**	**25.84**	**83.0**	**0.03**	3.07	50.0	0.19
Thalamus - Brain Stem	14	−2.28	58.0	0.36	−10.02	39.5	0.66
Thalamus – Calcarine	14	−15.55	22.0	0.97	−11.54	30.0	0.92
Thalamus – Hippocampus	12	−9.04	36.0	0.59	−2.69	44.0	0.35
Thalamus – Parietal	12	4.62	56.0	0.09	0.02	31.5	0.34
Thalamus – Frontal	14	9.99	65.0	0.09	4.88	68.5	0.16
Brain Stem – Calcarine	16	−11.24	40.0	0.93	−1.15	39.5	0.93
Brain Stem – Hippocampus	12	−5.25	36.0	0.59	8.46	43.0	0.38
Brain Stem – Parietal	13	−3.08	45.0	0.51	5.48	31.0	0.16
Brain Stem – Frontal	15	11.35	59.5	0.51	14.20	76.0	0.07
Calcarine – Hippocampus	12	8.04	58.0	0.07	**10.10**	**60.5**	**<0.05**
Calcarine – Parietal	13	12.19	62.5	0.12	5.77	54.0	0.28
Calcarine – Frontal	**15**	**23.64**	**97.0**	**0.02**	**15.46**	**111.0**	**<0.01**
Hippocampus – Parietal	11	11.00	34.5	0.45	4.36	31.5	0.55
Hippocampus – Frontal	12	20.48	54.5	0.11	8.58	52.5	0.14
Parietal – Frontal	13	1.75	40.0	0.47	2.94	54.5	0.26

[a] Mean difference = (1)–(2).
[b] Wilcoxon signed rank S statistic, prob. > S.

the basal ganglia and hippocampus. The cerebellum also showed significantly higher I-Hg compared to the thalamus and frontal cortex, but no significant difference was observed compared to other cortical regions, the basal ganglia, hippocampus, or brainstem. Both the basal ganglia and calcarine cortex showed significantly higher T-Hg compared to frontal cortex. Calcarine cortex had significantly higher I-Hg compared to the hippocampus and frontal cortex. T-Hg and I-Hg concentrations in other brain regions were similar.

Match-paired comparisons between the anterior, middle, or posterior calcarine cortex showed no significant differences, nor were there differences between any part of the calcarine cortex and non-calcarine occipital lobe.

Hair T-Hg (first cm) was significantly correlated with blood T-Hg ($\rho = 0.56$, $p = 0.01$, $n = 19$) and blood MeHg ($\rho = 0.72$, $p = 0.03$, $n = 9$). All brain T-Hg levels were highly correlated with one another (lowest $\rho = 0.76$, $p < 0.01$; highest $\rho = 0.98$, $p < 0.01$). When comparing the same individuals (i.e. individuals with available measurements in all major brain regions as well as blood T-Hg and hair T-Hg, $n = 10$), no significant correlations were observed between blood T-Hg and T-Hg in any major brain region, but T-Hg from the first cm of hair was correlated with T-Hg concentrations in all major brain regions except for the brainstem and hippocampus (Table 3). Correlations between blood T-Hg and hair T-Hg with MeHg in the brain regions were similar.

T-Hg concentrations in the liver and kidneys were highly correlated ($\rho = 0.75$, $p < 0.01$, $n = 16$). Significant correlations were observed between blood I-Hg and the renal medulla ($\rho = 0.65$, $p = 0.04$, $n = 10$). Both blood and hair T-Hg were correlated with T-Hg in the renal cortex ($\rho = 0.56$, $p = 0.03$, $n = 16$; $\rho = 0.61$, $p = 0.02$, $n = 14$ respectively).

The distributions of brain T-Hg concentrations in the major brain regions of the 5 individuals with the highest whole brain T-Hg concentrations are shown in Fig. 4. Among 4 of the 5 individuals, the greatest concentration of T-Hg is found in the cerebellum or basal ganglia.

Brain regions were ranked as containing the highest, second-highest, and third-highest concentrations of T-Hg for each individual and visualized in Fig. 5. For 7 individuals, T-Hg concentrations were highest in either the cerebellum ($n = 4$) or basal ganglia ($n = 3$). Either of these two brain regions was ranked as having the second-highest T-Hg concentrations in 5 out of 11 individuals.

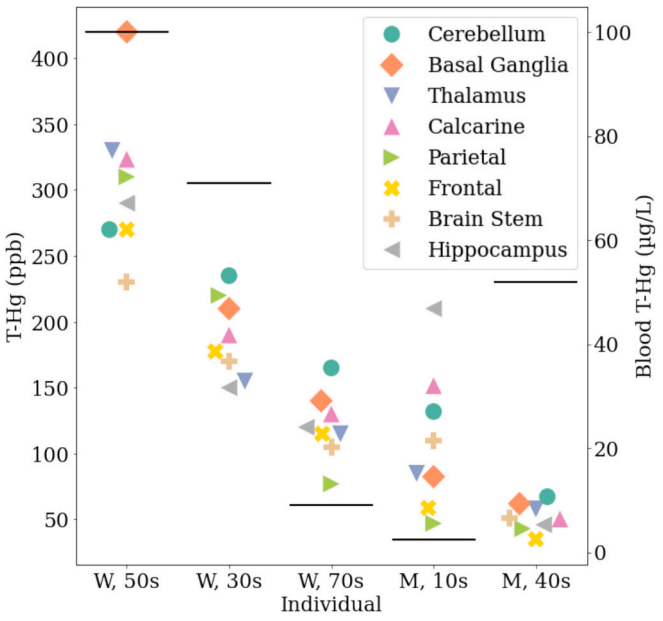

Fig. 4. Distribution of total mercury concentrations in 8 brain regions for the 5 individuals presenting the highest total brain T-Hg. Individuals are plotted on the x-axis in descending order according to whole-brain T-Hg. Blood T-Hg levels are represented by a horizontal black line. In total, 11 individuals' autopsy reports included Hg measurements for all major brain regions. Fig. 1 in supplemental material shows T-Hg in the same brain regions and blood for the remaining 6 of 11 individuals.

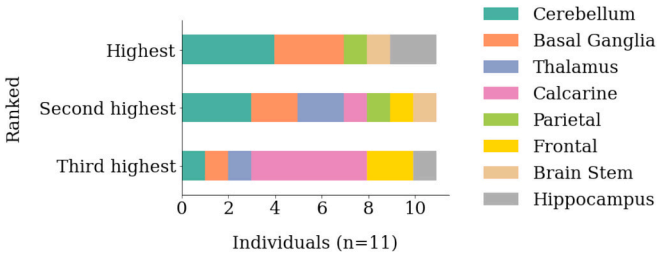

Fig. 5. Ranking of brain regions according to total mercury concentration. Eight brain regions of interest were ranked from highest (1) to lowest (8) T-Hg for each individual independently ($n = 11$), and those ranked in the top three were plotted.

4. Discussion

To our knowledge, this is the first study to publish data on the distribution of Hg concentrations in the brain, blood, hair and organs from autopsy reports of persons from Grassy Narrows First Nation. These findings are based on a decade of measurements (1976–1986) taken 14–24 years after the uncontrolled discharge of Hg into their territorial river system first began, and 6–16 years after emissions were curtailed and Hg contamination was made public. Results show the presence of Hg in all brain regions, blood, hair and organs of all autopsied individuals. The highest brain T-Hg concentrations were found in the cerebellum and basal ganglia, while in the other organs, the highest T-Hg concentrations were in the kidneys.

In 1975, clinical and epidemiological studies carried out in Grassy Narrows showed a high prevalence of persons with signs and symptoms similar to Minamata Disease, including but not limited to: difficulty seeing, insomnia, exhaustion, visual disturbance, pain, numbness, and sensory disturbances in the limbs (particularly glove and stocking-type sensory disturbance), tremors, ataxia, motor functioning issues, forgetfulness, and impaired speech [26,28]. Although hair T-Hg levels decreased over time, both during and after the period of the present study, in 2002 and 2011, about half of the individuals ($n = 45$ and 73, respectively) were diagnosed with Minamata disease by Harada and colleagues [26,28]. Recent studies have associated past long-term Hg exposure at Grassy Narrows with sensory, motor, cognitive, and neuropsychiatric symptoms that continue to evolve over time

Table 3
Non-parametric correlations (Spearman's ρ) between T-Hg concentrations in blood and first centimeter of hair with T-Hg concentrations in each major brain region.

	T-Hg	Cerebellum	Basal Ganglia	Thalamus	Calcarine cortex	Parietal cortex	Frontal Cortex	Brainstem	Hippocampus
Blood T-Hg	**ρ**[a]	0.55	0.51	0.47	0.52	0.36	0.42	0.34	0.53
($n = 10$)	*p*	0.10	0.13	0.17	0.12	0.30	0.22	0.34	0.11
Hair T-Hg	**ρ**	**0.77**	**0.75**	**0.74**	**0.72**	**0.72**	**0.76**	0.61	0.61
($n = 10$)	*p*	<0.01	0.01	0.01	0.02	0.02	0.01	0.06	0.06

[a] NB: Nonparametric Spearman's ρ correlation tests were used.

[46,57,58,60].

The routine autopsies reported in the present study were carried out for causes of death unrelated to Hg poisoning. As a result, the T-Hg values observed in the present study probably underrepresent the upper range of T-Hg concentrations among people in Grassy Narrows following the discharge. Indeed, between 1975 and 1980, Wheatley reported that 78.6 % of individuals had mean annual individual maximum blood T-Hg measurements ≥20 μg/L [85], and nearly 50 % of individuals from Grassy Narrows and neighbouring Wabaseemoong sampled by the Ontario Ministry of Health in 1971 had blood levels greater than 100 μg/L [76]. By contrast, in the present study, only 23.8 % (5 of 21 of individuals) had blood T-Hg measurements ≥20 μg/L.

Cerebellar lesions are known to be one of the major neural hallmarks of MeHg poisoning [20]. Though preferential accumulation in the cerebellum is not consistently found across autopsy cohort studies [50], significantly elevated levels of cerebellar T-Hg relative to other brain regions are often reported in populations with both high and low dietary MeHg exposure [53]. Particularly high cerebellar T-Hg concentrations were also noted in random brain autopsy studies of apparently healthy populations in the US [23,44,51].

Basal ganglia measurements of Hg are less frequently reported in the neural autopsy literature. However, consistent with our findings, Lapham's 1995 study of neonates from the Seychelles Islands found higher T-Hg means in the basal ganglia/thalamus, cerebellum, and pons/medulla, compared to cortical regions [36]. Autopsied infants and adults from the 1972 Iraq MeHg epidemic showed considerable variation in the T-Hg and I-Hg concentrations of the basal ganglia relative to other brain regions [3]. Moreover, non-human primates exposed to MeHg for 1–3 years had notably high T-Hg levels in the caudate nucleus (of the basal ganglia), in addition to the insula and calcarine cortex [68].

A recent study found that two individuals with Parkinson's Disease (PD) had Hg in many more brain regions (including parts of the basal ganglia) than both Hg-exposed and Hg-unexposed individuals without PD [52]. Given the common experience of atypical Parkinsonian-like symptoms in many individuals exposed to Hg, including the range of extrapyramidal signs currently observed in the community of Grassy Narrows (tremors, balance impairment, limb pain and weakness) [57,58], the present findings suggest the need for a closer examination of the role of basal ganglia damage in the onset and development of Hg-related motor dysfunction.

While little is known about the health status of the deceased persons in the present study, an archived Ontario Ministry of Labour report from 1977 [67] contained results from extensive clinical examinations for two autopsied individuals in Grassy Narrows prior to their death in 1976. One individual was reported to have had a mild static tremor, ataxia (inability to hop on one foot), and dysdiadochokinesia (inability to perform rapid alternating movements). Upon autopsy the following year, this individual was found to have had cerebellar degeneration as well as elevated levels of T-Hg in the cerebellum (vermis T-Hg = 160 ppb), calcarine (T-Hg = 74 ppb), and brainstem (T-Hg = 86 ppb).

Around the same time as these autopsies were performed, Wheatley and colleagues reported the autopsy data of a 79-year-old Cree patient from northwestern Québec for whom fish was a major dietary component. His cerebrum and cerebellum T-Hg concentrations were 320 ppb and 400 ppb respectively, which are similar to the maximum values found in the present dataset [84]. Two years prior to death, he had been assessed for signs and symptoms of Hg poisoning; the authors reported severe visual field restriction, sensory neuropathy, hand tremors, bilateral hearing loss, diminished reflexes, intention tremor, bilateral impairment of rapid alternating movements, severe reduction in perception of vibration sense, impairment of finger-to-nose coordination, gait ataxia, and visuomotor coordination [84]. Despite thoroughly documenting these signs and symptoms, medical authorities at the time qualified the diagnosis of mercury poisoning as "elusive" [84].

It is likely that brain I-Hg in this population largely derives from in situ demethylation because the majority of Hg exposure is through fish consumption [21]. In general, the inorganic fraction of T-Hg was approximately 25 % across brain regions and individuals, and much higher in the liver, heart, and kidney. The high concentrations and low organic fractions of T-Hg in the heart, liver, and kidneys are consistent with the known process of demethylation in the liver, and the accumulation of I-Hg in both the liver and kidneys [33,40,54,86].

Both T-Hg and I-Hg brain measurements in the present study correlated more strongly with hair T-Hg than blood T-Hg, which is consistent with known mechanisms of MeHg disposition. Scalp hair accumulates MeHg to a high degree, acting as a pathway of elimination [10]. Takeuchi estimated the half-life of MeHg in the brain to be 230–240 days [20,72], though the MeHg half-life across individuals is thought to range widely [62]. By contrast, the half-life of I-Hg in human brains may be on the order of several years to several decades [15,29,63,69,73].

While it is useful to situate the brain and organ Hg findings of the present study within the existing autopsy cohort literature, several important caveats apply. Firstly, the predominant sources of MeHg and I-Hg vary from population to population and can result in different distributions and speciation patterns in the brain and other tissues. Common sources of MeHg include freshwater and marine fish, as well as marine mammals, each of which has a different nutrient profile that may affect the bioaccessibility and toxicity of MeHg [24,48] and likely its distribution in the body [43]. Moreover, I-Hg exposure through industrial pollution, individual occupation, or dental amalgams can affect relative levels of MeHg and I-Hg in the brain [7]. Lastly, the procedures and techniques used to measure tissue mercury differ from study to study. Autopsy cohort studies of brain and organ Hg span a 50-year period, and strategies for reducing measurement error have changed over time [9,38,41], complicating the comparison of recent measurements with those taken several decades in the past.

Despite these caveats, it is interesting to note that, in general, while overall brain T-Hg concentrations varied across individuals, they were significantly higher than those reported for coastal populations with background levels of Hg exposure, such as in Denmark, Poland, and Sweden [4,25,53], as well as an urban population with low to moderate fish consumption near the Madeira river basin in the Western Amazon [16]. While median values in the present study were comparable to certain marine fish-eating communities [10,36,50,66,70], it should be noted that in some cases the highest brain T-Hg measurements in the present study were several times higher than the maxima found in these populations. Maximum brain T-Hg values in the present study were lower than those reported for an Indigenous population in Greenland that consumes marine fish and mammals [53] and were one to two orders of magnitude lower than some reported patients with severe Minamata disease in Japan [20,74,78]. Notably, some cortical measurements in the present study were similar to those reported for residents on the coast of Japan's Shiranui Sea in the 1970s and 1980s, whose average cerebral T-Hg levels had declined from approximately 10,000 ppb to 100 ppb from 1960 to 1980, and who continued to experience distal paresthesias of the extremities and lips even 30 years after the cessation of Hg exposure emanating from Minamata Bay [18].

T-Hg concentrations in the liver, kidney, and heart in this population were generally an order of magnitude higher than background values in autopsies performed in Poland [25,37] and Norway [34]. The elevated T-Hg levels in the renal cortex, renal medulla, liver, and heart were comparable to those found in marine fish-eating populations in Greenland [33], the Faroe Islands [34], Sweden [47], Korea [87], the Netherlands [1], and Japan [45,70].

The main strength of this study was the ability of the research team to access historic autopsies from a population with high Hg exposure from fish consumption, made possible by the leadership of Grassy Narrows First Nation, who negotiated with government ministries to obtain the autopsy reports of people from their community. The research was carried out as an academic-community partnership based on the principles of ownership, control, access, and possession of First Nations' data [OCAP Principles, a registered trademark of the First Nations

Information Governance Centre (FNIGC)]. This study of a cohort of historical autopsies is significant due to the relative rarity of detailed, regional brain measurements in mercury-exposed freshwater fish-eating populations. The relative measurements of T-Hg across brain regions or organ tissues within the same individual may be more reliable than absolute concentrations, because of methodological variation between autopsies and over the years. The present study's use of *within-subject* paired and ranked comparisons across brain regions therefore produced a reliable analysis of individuals' regional distributions.

There are several limitations to the present study. First, these historic data, from individuals autopsied for reasons unrelated to mercury exposure, contain no information about the health status, lifestyle, and dietary habits of individuals, nor was it possible to determine the cumulative duration of an individual's residence in Grassy Narrows. No information was available about overall fish consumption patterns, nor the presence of dental amalgams for these individuals. These unknowns limit our ability to draw conclusions about the relationship between diet, levels of Hg exposure, and brain and organ tissue Hg concentrations for the autopsied individuals.

Importantly, since the autopsy dataset reflects the methodology of several coroners over a period of 10 years, many individuals had Hg measurements taken from only a few brain locations, and brain samples were preserved, sampled, and measured in an inconsistent manner across individuals. To minimize the overrepresentation of individuals with a greater number of available measurements, several exclusion criteria were applied. Since individuals often had only a single measurement taken for most major brain regions, and because subregion measurements were similar within a given major brain region, it was appropriate to average across brain subregions to produce an estimated value in cases where multiple measurements were taken.

In this community, Hg exposure was highest in the late 1960s to early 1970s when most families ate fish every day, after which both Hg concentrations in fish as well as fish consumption declined [49,79,82]. It should not be assumed that individuals in the present study had reached steady-state concentrations in the brain or organs. Considerable inter-individual variability is introduced by different patterns of long-term and recent fish consumption, as well as idiosyncrasies in Hg processing and excretion. The distribution of MeHg and I-Hg throughout body tissues at time of autopsy is just one snapshot of the dynamic process of consumption, tissue distribution, demethylation, and excretion.

5. Conclusion

This study shows that Hg diffuses throughout the brain, and that it was present in the brains and organs of individuals from Grassy Narrows between the years 1976 and 1986 at levels much higher than those of populations with background exposure. Within the brain, the highest levels of Hg were found in the cerebellum and the basal ganglia. While Hg accumulation in the cerebellum has been documented, the basal ganglia has seldom been an object of interest in the Hg literature. The present findings moreover suggest the need for a closer examination of the role of the basal ganglia in the onset of Hg-related disorders. These historic brain measurements are valuable for understanding health challenges faced by the population of Grassy Narrows today.

CRediT authorship contribution statement

J.L. Lee: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Formal analysis. **M. Fraser:** Methodology, Formal analysis, Data curation. **A. Philibert:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Formal analysis, Data curation. **D. Saint-Amour:** Writing – review & editing, Methodology, Formal analysis, Data curation. **D. Mergler:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **M. Fillion:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Formal analysis, Data curation.

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Appendix A. Supplementary data

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