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IS MRI-BASED VOLUME A MEDIATOR OF THE ASSOCIATION OF CUMULATIVE LEAD DOSE WITH COGNITIVE FUNCTION?

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Is MRI-based Volume a Mediator of the Association of Cumulative Lead Dose with Cognitive Function?

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Abbreviations

MRI = magnetic resonance imaging

RAVENS = regional analysis of volumes in normalized space

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Abstract

This work considers the pathway through which past occupational lead exposure impacts cognitive function using cross-sectional data. It is motivated by studies linking cumulative lead dose with brain volumes, volumes with cognitive function, and lead dose with cognitive function. It is hypothesized that the brain regions associated with lead mediate a portion of the association between lead dose and cognitive function. The data were derived from an ongoing study of 513 former organolead manufacturing workers. Using MRIs, a novel analysis was performed to investigate mediation. Volumes associated with cognitive function and lead dose were derived using registered images and used in a subsequent mediation analysis. Cumulative lead dose was associated with adverse function in the visuo-construction, executive functioning and eye-hand coordination domains. Of these, there was strong evidence of volumetric mediation of lead's effect on cognition in the visuo-construction domain, a moderate amount for eye-hand coordination, and limited evidence for executive functioning. A second path analysis based approach was also performed. To address the possibility that chance associations explained these findings, a permuted analysis was conducted, the results of which support the mediation inferences. The approach to the evaluation of volumetric mediation may have general applicability in epidemiologic neuroimaging settings.

MeSH headings: cognitive manifestations; epidemiologic factors; epidemiologic methods; lead; magnetic resonance imaging; spectrometry, X-ray emission

We previously reported that past occupational exposure to organic and inorganic lead was associated with a decline in cognitive function (1) and with variation in the volume of brain structures as measured with magnetic resonance imaging (MRI) (2). Specifically, past cumulative absorption of lead, estimated by measurement of tibia lead (by ^{109}Cd-induced X-ray fluorescence), was associated with pronounced longitudinal decline in verbal memory and learning, visual memory, and executive function, and with variation in volume of total brain, parietal white and gray matter, temporal white matter, and two relatively small paralimbic system structures (cingulate gyrus, insula), among others. These findings raise questions about the extent to which variation in cognitive function measures that are associated with tibia lead are mediated through brain volumes measured by MRI.

Our previous work indicated that (peak cumulative) lead dose was associated with persistent and possibly progressive changes in the brain, both in the terms of cognition and brain structure, long after lead levels had declined in brain and blood (1-9). Based on these findings, we hypothesized that the brain regions associated with lead should mediate a portion of the association between lead and measures of cognitive function, recognizing that MRI only measures volume differences, not neurobiological and more subtle changes to brain structure. For this paper, we refer to these as overt (i.e., variation in MRI volumes) and covert (i.e., not detected by MRI) effects of lead (figure 1). More specifically, we hypothesize that variation in lead dose is associated with measurable variation in brain volume that, in turn, mediates variation in cognitive function. The variation in cognitive function attributable to lead that is not mediated by volume differences is assumed to be due to covert changes.

Mediation is often assessed from a comparison of results from longitudinal models with and without the hypothesized mediator (10). In our case, we assume that cognitive function is mediated through brain structure and neurobiology, whether or not we are able to observe all aspects of mediation. It is hypothesized that a component of the cross-sectional variation in brain volume associated with lead dose mediates a decline in cognitive function. We argue that this decline can be assessed, indirectly, by variation in cognitive function at cross-section. That is, because our evidence indicates that the effect of lead is at least persistent, and possibly progressive, the variation in cognitive function observed at cross-section incorporates historical changes attributable to past lead exposure, as well as other factors; the same assumption holds for MRI measures of volume. Given this framework, we test the hypothesis of mediation using cross-sectional measures of historical lead dose, brain volumes, and cognitive function. We present a voxel-by-voxel analysis to understand mediation that combines the attractive qualities of region of interest analysis while not being constrained by anatomical boundaries. Finally, we propose a method using permuted analysis that addresses inherent limitations in the voxel-based method and the traditional approach to evaluation of mediation.

MATERIALS AND METHODS

Study Population, Design, and Data

Overview. The data for this manuscript were derived from an ongoing prospective study of past occupational lead exposure and its associated health effects in central nervous system structure and function. Subjects were recruited from a chemical manufacturing plant that previously produced gasoline additives (7). Subject recruitment occurred in two phases between 1994 and 2003. Annual tests of

neurobehavioral function were performed. Current tibia lead was measured by ^{109}Cd-induced K-shell X-ray fluorescence in the third year for subjects recruited in Phase 1 (1994 to 1997) and in Phase 2 (2001 to 2003). Additional exposure information, such as the duration of exposure and the time since the last exposure, were also collected. Brain MRIs were collected during Phase 2. Detailed methods for Phase 1 and Phase 2 can be found in (2, 3) while the relevant aspects are summarized below. The study was reviewed and approved by the Johns Hopkins Bloomberg School of Public Health Committee on Human Research and written informed consent was obtained from all participants.

Subject recruitment. Individuals recruited for this study were former workers in the organolead area of a chemical plant, involved in the manufacture of tetraethyl lead from 1923 to 1991 and tetramethyl lead from 1960 to 1983, but were not occupationally exposed to lead at the time of study enrollment. All study participants were previously employed in the facility on or after January 1, 1950, were male, and were between the ages of 40 and 70 years in 1995. In Phase 1, a total of 703 former lead workers were enrolled and completed one to four visits. In Phase 2, another 276 former lead workers were enrolled and completed one or two visits. During Phase 2, MRIs were completed on 589 of the 979 former lead workers. Tibia lead was measured on 532 of the 589 individuals who completed MRI acquisition. Analysis was limited to the 513 subjects who had no errors in the processing of their images and had key covariate data. One subject was eliminated because of a potential neurological disorder. Cognitive function did not differ by MRI status and the relations of tibia lead with neurobehavioral test scores did not differ in those with and without MRIs (2).

Data collection. Data collection, cognitive assessment, and MRI acquisition protocols for the Phase 1 and Phase 2 studies have been previously described (1, 2). All subjects were scanned on the same General Electric 1.5 T Signa Model. Neurobehavioral test scores were aggregated into six cognitive domain scores (table 1), as previously described (11) according to neuropsychological theory and empirical evaluation of inter-test correlations and variation. Before creating domains specific measures, individual test scores were normalized. Current tibia lead was used to derive peak tibia lead levels, the estimated level at the end of occupational lead exposure, by previously published methods (3, 12). Peak tibia lead was found to be the lead dose measure most associated with cognitive test scores (3), decline in cognitive function over time (1), brain volumes, and white matter lesions (2).

Image processing. Images were preprocessed using previously published methods (2, 13) and subsequently segmented (into gray matter, white matter, and cerebrospinal fluid) using a Bayesian algorithm (14). Regional analysis of volumes in normalized space (RAVENS) was used to elastically warp brain images into a standard template space while retaining volumetric information (15). The RAVENS images contained absolute volumes in standardized Talairach space (16), with separate gray and white matter images, that provide the means for inter-subject voxel-wise analysis.

The principal benefit of the so called voxel-based morphometry approach, is the ability to assess associations of predictor variables in highly localized volumetric analyses without relying on anatomically constrained regions of interest (17, 18). In contrast, analysis of anatomy-based regions of interest requires assumptions on the resolution of the anatomy to be considered. For example, total brain volume can be

decomposed into total gray and white mater volumes, which can be decomposed into smaller substructures, and so on. Voxel-based morphometry, i.e. the voxel-by-voxel statistical analysis of the RAVENS images, avoids challenges to these assumptions, as well as complications from the anatomical definitions required by traditional region of interest-based analysis, and enables an unbiased evaluation of morphometry and post hoc determination of regions of interest that are not known *a priori*. (In this study, these are regions that mediate the association between lead exposure and cognition).

Statistical Analysis

Overview and justification. The analysis followed by recasting the highly multivariate imaging data into targeted univariate summaries, which were used in a mediation analysis. Below, we briefly overview the analysis methods followed by detailed discussions of the creation and analysis of the summaries.

Complicating matters is the amount of data in the RAVENS maps. We develop novel methodology for recasting the problem into the terms of the traditional mediation analysis using lower dimensional summaries. As a result, our approach will be largely exploratory, providing only indications of the existence and extent of mediation.

The analysis procedure followed three steps. In the first step, inter-subject lead- and domain-derived association areas were identified by regressing voxel volumes on peak tibia lead and cognitive domain scores, respectively. [The RAVENS value at a given voxel reflects the amount of grey or white matter in the vicinity of that voxel (13)]. Secondly, these association areas were used to create association masks, which were applied to each subject to obtain lead- and domain-defined subject-specific association volumes. Finally, these univariate volumes were used in a mediation analysis.

Mediation is typically assessed using repeated measures of the outcome and the mediator. Specifically, a general linear model of the effect of interest on the outcome is evaluated with and without the potential mediator. A change in significance, or drastic change in the magnitude of the effect, is evidence of mediation. Alternatively, path analysis has been used, where linear structural relationships are assumed between the outcome of interest, the mediator and remaining variables (19, 20). A close variant of the latter method uses two-stage regression model fits (10). We also note that consideration of mediation has been modernized by employing counterfactual reasoning (21, 22). We did not explore this latter approach, as our emphasis is primarily on the derivation of appropriate image analysis methodology for the subsequent investigation of mediation, and hence we rely on the most straightforward statistical methods for mediation analysis.

Therefore, mediation was assessed by first evaluating the association of peak tibia lead with the six cognitive domain scores, with and without the association volumes in the model. Secondly, path analyses were used to decompose the total effect of lead exposure on cognitive function into direct and indirect effects (see below).

Association volumes. The construction of the association volumes deserves special attention. Conceptually, the following volumetric regions are of primary interest: the volume most associated with peak tibia lead and the volumes most associated with the cognitive domain scores. The lead association volume was derived after a voxel-by-voxel regression analysis of the RAVENS maps with voxel-level volume as the outcome and peak tibia lead as the predictor. Separate regression analyses were performed with white and gray matter volumes as the dependent variables and peak tibia lead as

the predictor, adjusting for age. Because of imperfect registration and noise, the RAVENS maps were smoothed using a 10 mm full width at half maximum Gaussian smoother and the models were only fit at those voxels containing values for at least 400 subjects.

The voxels for the gray and white statistical parametric maps of the student's T-statistics for the lead effect below either the 0.001 or 0.00002 normal quantiles were used to create the association-masks. Note that interest lied in negative associations (increasing lead exposure implying a decrease in volume). The resulting masks have a value of zero for each gray or white matter voxel that was not significantly associated with lead across subjects and a one for each voxel that was. These masks were then applied to each individual's RAVENS gray and white matter maps. The voxel volumes within the mask for each subject were summed and expressed in mm^3 as the gray or white matter volume *for that subject* most strongly associated with PTL *across subjects*.

The cognitive domain association volumes were derived in exactly the same manner, with the following two exceptions. First, the cognitive domain scores were treated as the outcomes and the voxel-level volumes as the predictors in the voxel-wise regression models. Secondly, the statistical maps were created for the positive associations (increasing volume implying increasing cognitive function).

Evaluation of mediation. The association volumes for gray and white matter and for lead and cognitive domain scores were included and excluded (separately) in models relating lead exposure to the cognitive domain scores, adjusting for covariates [age, visit number, education (less than high school, high school graduate, some college, college grad), and cognitive function tester]. The impact of the inclusion of the

association volumes on the magnitude and significance of the regression coefficient for peak tibia lead was then evaluated.

It should be emphasized that the models considered absolute, not proportional, associations of brain volumes with lead and cognitive domain scores. To investigate proportional changes, we also considered models with total gray and total white matter included as covariates. Finally, we also considered models with body habitus measurements, such as height, weight, and body mass index, as covariates, to control for variation in intrinsic brain size.

A second analysis derived the proportion of the total effect of lead that was a direct effect through the use of the following path analysis models:

(Eq. 1) Cognitive domain score = $B_0 +$ B_1 PTL + B_2 ROI + B_3 Age + B_4 Visit + B_5 Educ + B_6 Tech + Error

(Eq. 2) ROI = $\gamma_0 + \gamma_1$ PTL + Error

where PTL is peak tibia lead, ROI is region of interest association volume, Educ is years of education, and Tech is cognitive tester (included because was found to be an important confounding variable in prior analysis (1, 3)). The direct effect is defined to be B_1, the indirect effect as $\gamma_1 B_2$, the total effect as $B_1 + \gamma_1 B_2$, and the proportion of the total effect that is direct as $B_1 / (B_1 + \gamma_1 B_2)$. This and the subsequent regression models and path models were estimated assuming mutual independence and normality of the errors using the language R (23). The voxel-wise regression models were verified and the Gaussian smoother was applied using the SPM package for Matlab version 6.5.

One limitation of our method arises from multiplicity concerns. The same data are used to create the association volumes and to evaluate mediation, with the possibility that chance associations were responsible for the results. To address this concern, the association masks were recalculated with the labels linking subjects to their images permuted. In this way, the subsequent mediation analysis, performed in the same way as previously described, was based entirely on spurious correlations of lead or cognitive domain scores with voxel volumes. One hundred such permutation replications were performed.

RESULTS

Description of study subjects. The 513 subjects in the analysis were all male, and had an average: age of 60.4 years, 8.6 years of occupational exposure to lead, 18.0 years since last exposure, and peak tibia lead of 24 μg lead per gram bone mineral (table 2). The average total brain volume was 1,150.3 cm^3, divided into 588.4 cm^3 for gray matter and 561.9 cm^3 for white matter. The majority of study subjects were current alcohol users (69%), did not have the apolipoprotein E ε4 allele (73%), had at least some high school education (59%), were white (92%), and were previous tobacco users (51%) (table 3).

Correlations among important predictor variables are summarized in table 4, including the association volumes (p-value threshold of 0.001), age, peak tibia lead, and the cognitive domain scores. Correlations with gray matter association volumes are above the diagonal while those with white matter are below. As expected, peak tibia lead and age were negatively correlated with all of the cognitive domain scores and association volumes. The association volumes were strongly correlated to each other,

likely due to the high degree of variation in individual brain size. Of note, the verbal memory and learning domain showed lower associations overall. Also, the cognitive domain scores were only modestly correlated with one another.

Association volumes. The association volumes are graphically displayed on coronal, sagittal, and transverse "glass brain" projection images in figure 2. The association volume with peak tibia lead was larger for white matter than for gray matter, and the lead association volumes were relatively small compared to the domain volumes, except for the verbal memory and learning domain (table 5). For the domain association volumes, visuo-construction domain was the largest gray matter region, while processing speed was the largest in white matter. Performance in verbal memory and learning region was not associated with gray or white matter volumes. The association volumes for both lead and cognitive domain scores were very small in the representative permuted analysis, except for gray matter processing speed volumes, which were still notably smaller than the actual volumes.

Evaluation of mediation. Evaluation of mediation is principally of interest when the total effect is significant. In regression models adjusting for covariates, peak tibia lead was associated with worse performance in visuo-construction, executive functioning, and eye-hand coordination (figure 3, which summarizes point estimates and 95% confidence intervals for the peak tibia lead coefficient in associations with the six cognitive domain scores). Traditional mediation analysis considers the impact on the total effect (represented by the first bar plot for each domain, on the left) after inclusion in the regression models of the potential mediators (represented by the next four bar plots for each domain). The figure displays the magnitude (and confidence interval) of

the lead association after addition of the lead and domain association volumes, separately for gray matter and white matter.

Some evidence of mediation was present in all three of the domains with a significant total effect of peak tibia lead. However, the visuo-construction domain showed the most striking evidence of mediation, as the association of tibia lead with cognitive function decreased in magnitude and statistical significance after inclusion of either the lead or domain association volume, for both gray and white matter. In the related path analysis with structural equations models, the resulting proportion of the total effect of peak tibia lead that was direct was 0.47, 0.48, 0.66, and 0.60 after inclusion of lead and domain association volumes, for gray matter and white matter, respectively (corresponding to the left-to-right ordering of the bar plots in figure 3).

Relatively weaker evidence of mediation was demonstrated in the executive functioning and eye-hand coordination domains. For executive functioning the strongest suggestion of mediation was in the lead association volume for gray matter, with the peak tibia lead association becoming non-significant after its inclusion. After inclusion of the remaining association volumes, there was weaker evidence of mediation, and the direct effect of peak tibia lead remained significant. Mediation through gray matter volumes was stronger than through white matter volumes, and through lead volumes greater than through domain volumes, despite the much smaller average sizes of the lead volumes than the domain volumes. The resulting proportion of the total effect of peak tibia lead that was direct was 0.61, 0.61, 0.73, and 0.74, corresponding to the ordering above (and in figure 3).

Eye-hand coordination showed moderate evidence of mediation, with the lead effect becoming barely non-significant after the inclusion of the association volumes. More striking evidence of mediation was present in the white matter association volumes. The corresponding proportion of the total effect of peak tibia lead that was direct was 0.73, 0.77, 0.72, and 0.71, in the same order as above.

The permuted analysis showed no evidence of mediation. The gray matter lead association volumes did not reverse the total effect in 82%, 100%, 100% of the simulations for visuo-construction, executive functioning and eye-hand coordination domains respectively. The corresponding percentages were 97%, 100%, 100% for white matter lead association volumes, 71%, 100%, 100% for gray matter domain association volumes and 79%, 100%, 100% for white matter domain association volumes. These results confirm the hypothesis that the evidence of mediation was not based only chance associations.

DISCUSSION

Of the three domains in which there was an association of peak tibia lead with test scores, the results suggest strong evidence of mediation in the visuo-construction domain, moderate evidence of mediation in the eye-hand coordination domain, and weak evidence of mediation in the executive functioning domain. The remaining cognitive domains showed no association with peak tibia lead, hence the mediation question was not of interest.

The approach to identification of the lead and cognitive domain association volumes implemented in this manuscript offers a complementary method of addressing the question of mediation to using anatomically defined volumes. Moreover, using

flexible voxel-wise regression models to define association volumes eliminates the decision of how finely to dissect the anatomically-based volumes, which can vary in size from total brain volume to the volume of small limbic substructures. In addition, our approach explicitly targets potential mediation volumes that are most likely affected by lead exposure and most strongly associated with cognitive domain function. In contrast, anatomically-based volumes aggregate relevant and non-relevant volumes within a specific anatomical structure that may not be related to either lead or function. Another notable benefit of the proposed analysis is the high degree of data reduction for the subsequent evaluation of mediation.

A principal concern regarding the construction of the association volumes is that chance associations could suggest mediation not actually present. The novel permutation analysis demonstrated that the evidenced mediation is likely more substantive.

A related analysis, which we relegate to future work, considers voxel-by-voxel path analysis. A concern with this approach, however, is that the potential mediating volumes are diffuse, and may offer little information regarding localization of the mediating effect at the voxel level. The current approach offers a compromise between the rigidity of anatomically-based structural volumes and the extreme localization that would be attempted by a voxel-wise path analysis.

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Figure captions

Figure 1. Schematic summary of relations of lead dose, brain structural volumes, and cognitive function. Citations refer to published manuscripts that have reported various parts of these relations. The current manuscript presents an analysis to evaluate mediation directly.

Figure 2. Coronal, sagittal, and transverse glass brain projection maps for associations of peak tibia lead or cognitive domain scores with gray matter (top) or white matter (bottom) voxels, adjusted for age. The different shading represents the two statistical thresholds (p-values of 0.001 [solid] or 0.00002 [cross-hatched]). Abbreviations are as in figure 2.

Figure 3. Point estimates and 95% confidence intervals for the association of peak tibia lead with cognitive domain scores per one μg/g increase in peak tibia lead before (labeled “Unadj” for unadjusted) and after inclusion of the lead (labeled “PTL ROI” for peak tibia lead region of interest volume) and cognitive domain (labeled “Domain ROI”) association volumes, separately for gray matter and white matter. The regression models also included age, an indicator for visit number (first vs. not first), the presence of the APOE ε4 allele (yes vs. no), lead exposure duration (years), years of education, testing technician, years since last exposure, smoking status (never, previous, current), and drinking status (never, previous, current). Estimates (standard errors) are given above or below confidence interval bars.

TABLE 1. Definition of cognitive domains used in analysis, former organolead workers study, Delaware and New Jersey, 2001-2003.

Domain	Tests
Visuo-construction	Rey complex figure, copy task, and Block design from the Wechsler Adult Intelligence Scale
Verbal Memory and learning	Rey auditory verbal learning test immediate recall, delayed recall, and recognition, and serial digit learning
Visual memory	Rey complex figure delayed recall and symbol digit
Executive functioning	Purdue pegboard assembly minus both hands, Stroop C form minus A form, and trail-making test B minus A
Eye-hand coordination	Purdue pegboard dominant hand, non-dominant hand, and both hands, and trail-making test A
Processing speed	Simple reaction time

TABLE 2. Summary statistics for continuous traits of the 513 former organolead workers included in the analyses, Delaware and New Jersey, 2001-2003.

Variable	Summary Mean (SD, min, max)
Age (years)	60.39 (7.93, 34.70, 78.30)
Brain volume(cm^3)	
Total	1150.32 (106.00, 733.56, 1487.99)
Gray	588.39 (60.05, 314.35, 762.85)
White	561.92 (59.03, 389.48, 748.22)
Domain scores	
Visuo-construction (VC)	-0.36 (1.03, -4.51, 1.73)
Verbal memory and learning (VML)	0.26 (0.80, -2.40, 1.87)
Visual memory (VM)	0.15 (0.92, -2.40, 2.19)
Executive functioning (EF)	-0.16 (0.76, -3.76, 1.64)
Eye-hand coordination (EHC)	-0.10 (0.88, -4.93, 1.61)
Processing speed (PS)	-0.16 (0.77, -4.39, 2.06)
Exposure duration years)	8.64 (9.83, 0.00, 52.14)
Peak tibia lead (μg Pb/g bone mineral)	23.99 (18.46, -13.02, 118.65)
Time since last occupational lead exposure (years)	18.01 (10.92, 1.50, 48.30)

TABLE 3. Summary statistics for categorical traits of the 513 former lead workers included in the analyses, Delaware and New Jersey, 2001-2003.

Variable	Summary [N (%)]
Alcohol use	
Never	19 (3.75)
Current	348 (68.77)
Previous	139 (27.47)
APOE genotype	
No ε4	365 (73.15)
At least one ε4	134 (26.85)
Education	
Less than HS	32 (6.25)
Some HS	303 (59.18)
Some college	154 (30.08)
College grad	23 (4.49)
Race	
White	473 (92.38)
Non-white	39 (7.62)
Technician*	
1	116 (22.92)
2	133 (26.28)
3	175 (34.58)
4	82 (16.21)
Tobacco use	
Never	153 (30.24)
Current	93 (18.38)
Previous	260 (51.38)
Visit number**	
1	170 (33.20)
2	9 (1.76)
3	25 (4.88)
4	47 (9.18)
5	257 (50.20)
6	4 (0.78)

***** The number of subjects receiving cognitive battery by each technician.

** The number of visits for cognitive function testing corresponding to the visit where MRI acquisition occurred.

Tabe 4. Pearson's correlations among study variables. Gray matter volumes are above the diagonal and white matter volumes below. The association volumes are indicated with larger boxes surrounding the axis labels. Abbreviations used: EF = executive functioning, EHC = eye-hand coordination, PSP = processing speed, PTL = peak tibia lead, ROI = region of interest volume, VC = visuo-construction, VM = visual memory, VML = verbal memory and learning. Domain and lead derived ROIs (constructed using statistical maps) are separated by boxes.

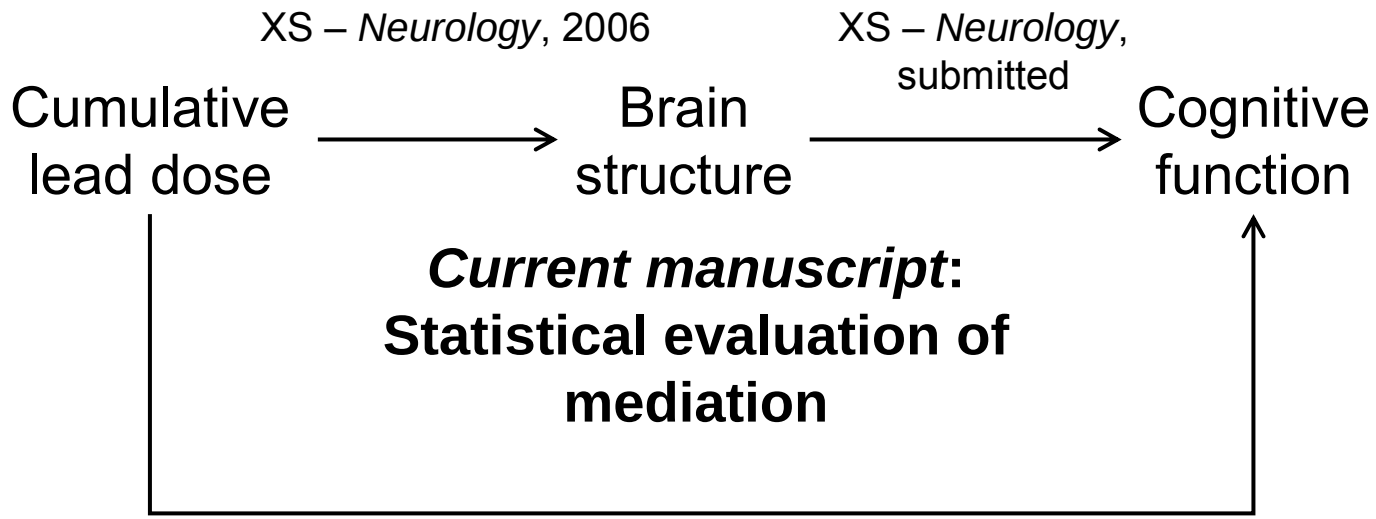
Gray	Age	PTL	VC	VML	VM	EF	EHC	PSP	PTL	VC	VML	ROI VM	EF	EHC	PSP	
PSP ROI	-.23	-.21	.25	.11	.24	.29	.27	.29	.82	.83	.57	.94	.89	.95		PSP ROI
EHC ROI	-.19	-.18	.22	.10	.21	.27	.29	.24	.75	.77	.57	.96	.82		.99	EHC ROI
EF ROI	-.40	-.30	.33	.13	.27	.41	.33	.29	.95	.97	.50	.80		.99	1.00	EF ROI
VM ROI	-.17	-.16	.22	.11	.28	.23	.21	.21	.73	.76	.59		.95	.95	.96	VM ROI
VML ROI	-.10	-.13	.17	.22	.22	.18	.20	.16	.44	.46		.79	.72	.74	.74	VML ROI
VC ROI	-.39	-.28	.38	.11	.28	.35	.30	.26	.92		.68	.92	.97	.95	.97	VC ROI
PTL ROI	-.50	-.40	.32	.15	.28	.38	.35	.29		.95	.69	.91	.98	.98	.98	PTL ROI
PSP	-.32	-.22	.36	.43	.38	.50	.58		.27	.25	.28	.26	.27	.28	.29	PSP
EHC	-.48	-.33	.40	.38	.39	.59		.58	.29	.25	.30	.25	.28	.31	.28	EHC
EF	-.44	-.33	.45	.47	.45		.59	.50	.29	.28	.29	.27	.31	.30	.29	EF
VM	-.31	-.23	.55	.51		.45	.39	.38	.22	.23	.27	.28	.23	.23	.23	VM
VML	-.22	-.18	.31		.51	.47	.38	.43	.11	.09	.25	.14	.11	.13	.12	VML
VC	-.33	-.24		.31	.55	.45	.40	.36	.24	.31	.23	.24	.25	.24	.24	VC
PTL	.45		-.24	-.18	-.23	-.33	-.33	-.22	-.30	-.24	-.24	-.22	-.26	-.27	-.25	PTL
AGE		.45	-.33	-.22	-.31	-.44	-.48	-.32	-.29	-.28	-.36	-.23	-.29	-.29	-.28	AGE
	Age	PTL	VC	VML	VM	EF	EHC	PSP	PTL	VC	VML	ROI VM	EF	EHC	PSP	**White**

TABLE 5. Summary statistics for the volumes associated with peak tibia lead and cognitive domain scores (using 0.001 p-value threshold), for gray matter and white matter, for both regular and a representative permutation analyses, 513 former organolead workers, Delaware and New Jersey, 2001-2003.

	Gray Matter Volumes* Mean (SD) cm^3		White Matter Volumes* Mean (SD) cm^3	
	Regular Analysis	Permuted Analysis	Regular Analysis	Permuted Analysis
Peak tibia lead association volume	9.24 (1.14)	0.01 (0.00)	37.33 (3.80)	0.02 (0.01)
Cognitive domain association volume				
Visuo-construction (VC)	109.36 (12.17)	1.21 (0.15)	72.61 (7.67)	0.62 (0.09)
Visual memory & learning (VML)	0.01 (0.00)	0.08 (0.02)	0.78 (0.15)	0.01 (0.00)
Visual memory (VM)	58.92 (7.65)	0.19 (0.03)	41.42 (4.88)	0.10 (0.01)
Executive functioning (EF)	86.93 (9.49)	0.66 (0.13)	96.45 (9.91)	0.20 (0.05)
Eye-hand coordination (EHC)	24.68 (3.08)	5.66 (0.65)	54.08 (5.69)	2.77 (0.38)
Processing speed (PS)	32.74 (3.86)	22.96 (3.89)	97.26 (10.13)	5.47 (0.80)

* The volumes were derived using a p-value threshold of 0.001 from statistical maps obtained by regressing voxel volumes from RAVENS images on either peak tibia lead or cognitive domain scores.

Figure 1



XS = cross-sectional analysis
LA = longitudinal analysis
EHP = *Environmental Health Perspectives*

Figure 2

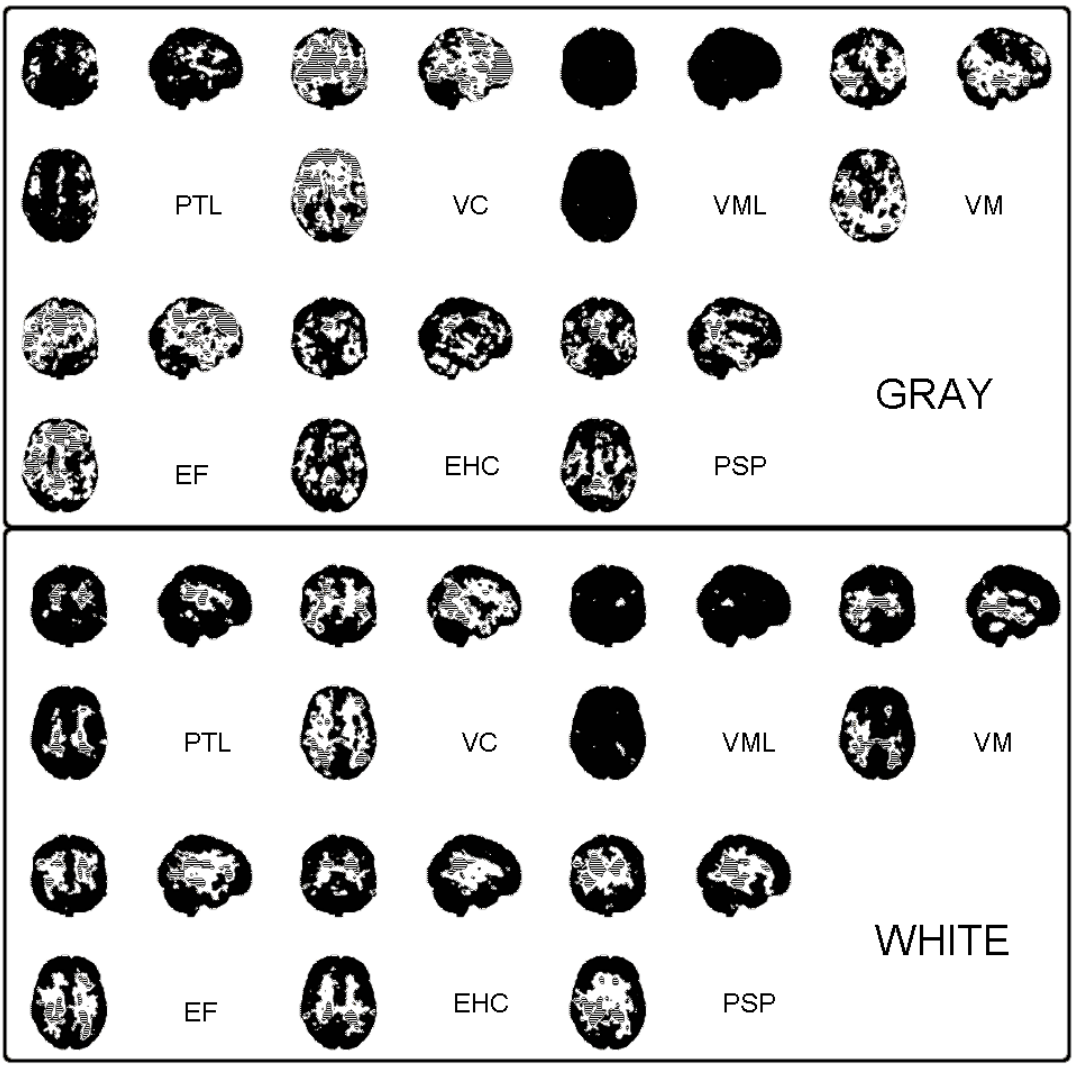
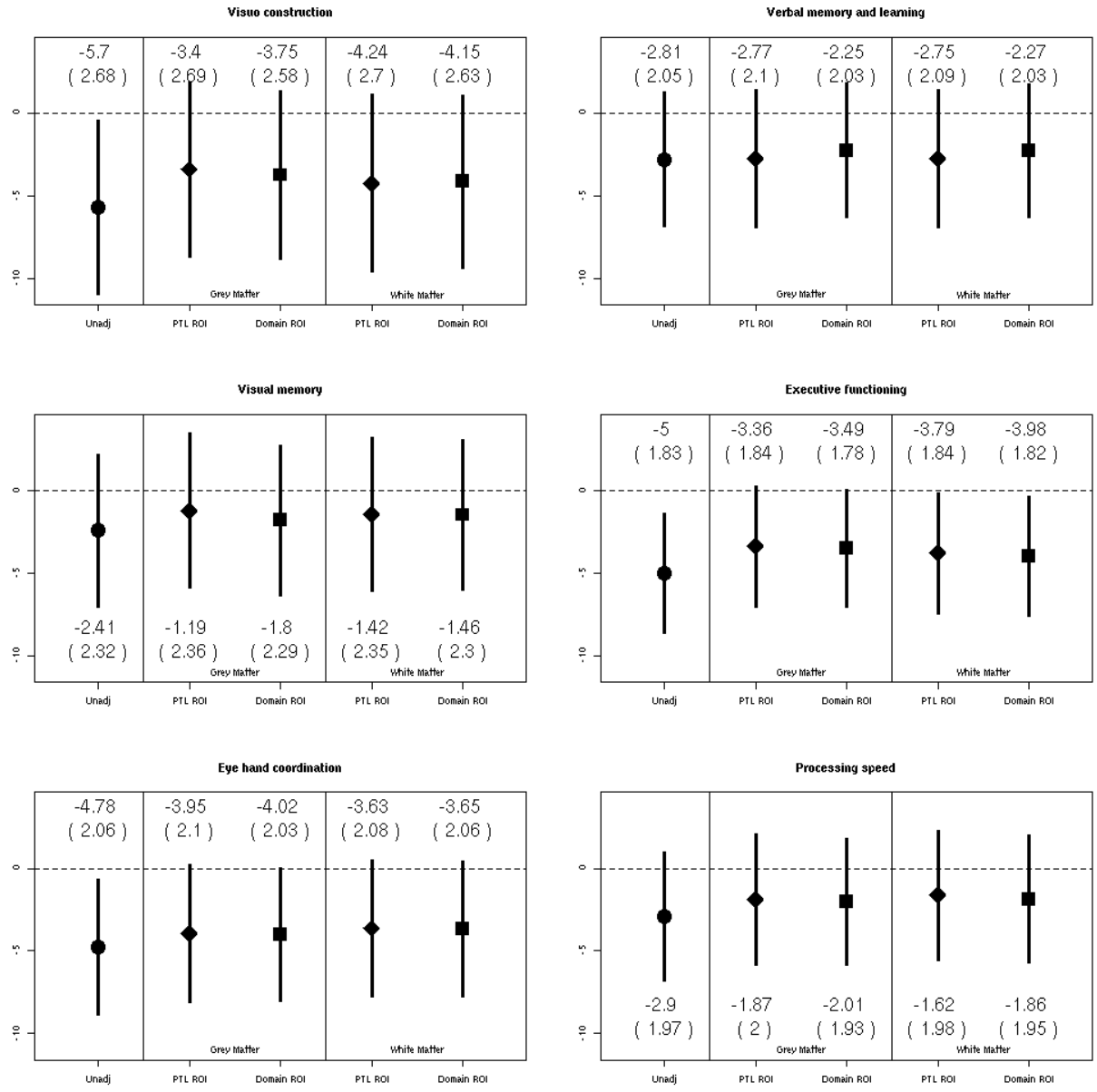


Figure 3



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