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Review

Resolving scientific controversy over smelter risks and neurodegenerative effects of metals

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Abstract: Although it is well known that metals pollution can cause neurotoxic effects, scientists are currently divided about the neurodegeneration hypothesis. That is, some scientists accept, while others fail to accept, the hypothesis that metals/metalloids, at exposure levels below those capable of causing neurotoxicity, can cause neurodegeneration—progressive or worsening neurological disease. Partly because of controversy over the neurodegeneration hypothesis, the US and other governments do not require cleanup of smelter-site metals, to the level (that many scientists say is) necessary to prevent site-caused neurodegenerative disease. The purpose of this review article is to help clarify and resolve conflict over the neurodegeneration hypothesis. This analysis (1) surveys the global problem of smelter-related metals pollution; (2) quickly gives an overview of metals pollution at one of the worst US Superfund or hazardous-waste sites, a former smelter in DePue, Illinois; (3) outlines the debate over the neurodegeneration hypothesis; and (4) assesses the current science on both sides of the neurodegeneration hypothesis by means of three classic methods of causal assessment: the mechanism, unification-coherence, and experimental-counterfactual methods. Using these classic methods, the authors (5) show that available scientific evidence argues for accepting the neurodegeneration hypothesis. This finding is significant because it suggests that much current science about smelters and metals' risks may be incomplete or flawed. It also shows that, as a result, there may be sound scientific reasons for strengthening environmental-metals standards.

Keywords: cause; coherence; mechanism; metal; neurobiology; neurodegeneration; neurotoxicity; smelter; unification

1. Introduction

1.1. Research background and framing the question for review

Globally, most soil-metals levels near current and former metals smelters exceed regulatory levels; all of the planet's highest-average-soil-metals concentrations are near current or former smelter sites [1,2]. In part as a result of smelter contamination, there has been a global "epidemic" of chronic metals neurotoxicity [3], especially in developing nations, but even in developed countries such as Austria, Canada, Japan, and the US [4]. In the US, roughly 5 million people, one-third children, live within a mile of nearly 1000 former smelters, 90 percent of which are not cleaned up and have soil-metals levels well above regulatory limits [5,6,7].

One reason for this neurotoxicity "epidemic" appears to be the causal controversy over the neurodegeneration hypothesis, the hypothesis that metals/metalloids, at exposure levels below those capable of causing neurotoxicity, can cause neurodegeneration, that is, progressive or worsening central-nervous-system disease. Of course, the US Environmental Protection Agency (US-EPA) and virtually all scientists recognize metal-caused neurotoxicity, that is, central-nervous-system damage from metals. However, some scientists and US-EPA officials fail to accept the neurodegeneration hypothesis C, metals-caused neurodegeneration [8].

Partly as a result of not accepting the neurodegeneration hypothesis, government has not imposed strict, timely metals-cleanup standards. For instance, at the DePue, Illinois and other former smelters, US-EPA standards for nearby residential soils require clean-up only to 400,000 ppb of lead [9]. Yet many scientists and the California EPA say serious neurobiological harm begins at soil-lead levels of 15 ppb [10]. The metals cleanup also is not timely at most former smelter site. For instance, in 1980, US-EPA closed the DePue facility. It warned that DePue is among the most hazardous 0.1 percent of US toxic sites because of nearly-century-long smelter releases of arsenic, barium, cadmium, cobalt, copper, iron, lead, manganese, mercury, nickel, silver, sodium, vanadium, and zinc that have contaminated the site, hundreds of offsite residences, and local public wildlands and waterways [9]. Yet for 34 years the community has waited for metals decontamination. Polluters have remediated only one onsite ditch. No offsite and residential-soil/water contamination has been remediated, and metals-contaminated water still flows into the large public recreational and fishing area of Lake DePue. Fighting over the neurodegeneration hypothesis is part of what is delaying site cleanup and allowing weak clean-up standards.

On one hand, local residents and many scientists accept this hypothesis and attribute increased DePue neurodegenerative diseases to soil/airborne metals from the former smelter. They cite a 19-year study that documented "significant exposure" to heavy metals and increased health harms among 2000 DePue residents, including 10 times the expected cases of multiple sclerosis or MS, a neurodegenerative disease [11]. They also cite numerous studies linking metals and neurodegenerative diseases such as MS, Alzheimer's (AD), Parkinson's (PD), and ALS or amylateral sclerosis [12-40].

On the other hand, site polluters, New Jersey Zinc and Exxon-Mobil (ZEM), the US-EPA, and some scientists do not accept the causal link between metals exposures and neurodegenerative disease. Instead they claim most neurodegenerative disease is "idiopathic" [41-44], of unknown cause. Or, as the US-EPA officially says, "there is not yet consensus regarding the causative agents" of excess neurodegenerative diseases that have appeared in DePue and at other smelter-metals sites [8].

1.1.1. Defining neurodegeneration

Although scientists may disagree about the neurodegeneration hypothesis, they agree on what neurodegenerative disease is. They say all neurodegenerative diseases have three common and necessary features NOP, as follows: chronic **neuroinflammation**, (increased rates of brain-cell death typically caused by) overproduction of reactive-oxygen species or **oxidative stress**, and increased levels of atypical/misfolded/damaged and therefore **toxic brain-protein assemblies** [45-49]. NOP occurs as direct, brain-protective responses to invading pathogens/toxins/metals. When NO induce P, P in turn produces even more NO, and they further increase P. As later paragraphs show, NOP thus causes a cycle of worsening neurotoxic effects, that is, neurodegeneration. In fact, P already has attained the status of "core biomarker" for diagnosing neurodegenerative disease. Even before clinical symptoms appear, tau and amyloid-beta proteins are overproduced in AD, for instance, while alpha-synuclein proteins are overproduced in PD. Core biomarker changes P, in cognitively-normal-but-at-risk individuals, are correlated both with their later being diagnosed with neurodegenerative diseases and with their levels of cognitive impairment [46,50].

Given the definition of neurodegenerative disease in terms of NOP, and the fact that P is "core biomarker" for neurodegenerative disease, clarifying the controversy over the neurodegeneration hypothesis includes assessing whether or not metals can cause NOP. This assessment, however, is complicated by several factors.

1.1.2. Factors muddying the neurodegeneration controversy

Although all metals can be deadly, their dose-response curves differ in ways that muddy the neurodegeneration hypothesis. For the dose-response curves of most metals/metalloids—those that have no biological role, such as arsenic, barium, cadmium, lead, mercury, nickel, silver, and vanadium [16,19,27,28,29,32,36,51,52]—scientists have never discovered a safe or threshold dose for harm. This "never-discovered-safe-dose" claim seems reliable because most of the no-threshold metals are among the 10-most-studied toxic chemicals, in terms of the numbers of experiment-based scientific publications, 600–1400 per metal, per year [3]. However, while neurodegeneration-hypothesis proponents claim consensus about no safe dose of no-biological-use metals, those who fail to accept this hypothesis often argue that a damage-threshold is likely, given bodily detoxification and antioxidant processes [53-59].

Another factor complicating debate over the neurodegeneration hypothesis is that the body requires tiny, trace amounts of at least 6 metals, cobalt, copper, iron, manganese, sodium, and zinc, to meet essential needs [60-63], although any further accumulation can be toxic [61,63-66]. Hence those who do not accept the neurodegeneration hypothesis use these trace doses, from foods grown in noncontaminated soils, to argue that small additional doses of metals need not cause neurodegenerative harm. However neurodegeneration-hypothesis proponents say that, even if biologically-needed metals have a tiny threshold dose, near-smelter residents typically have received exposures up to thousands of times greater [11]. Besides, the adult-maximum-daily-metal-intake levels (that pose no risk of adverse affects) are tiny, for instance, 10 μg cobalt [67] 10,000 μg copper; 45 μg iron; 11 μg manganese; and 40 μg zinc [62,63,68].

1.2. Research aim

The aim of this article is to assess the causal-scientific controversy over the neurodegeneration hypothesis. This aim is scientifically important because some scientists already claim to have shown that metals exposures (many from fossil fuels such as the particulate matter from vehicle exhausts) have induced IQ declines and premature neurodegenerative diseases, such as early AD and PD, in many upper- and middle-class urban children [50,69]. Yet residents living near smelters likely receive even higher metals exposures. If this article is correct, it has achieved its aim, to review the evidence and assess whether the neurodegeneration hypothesis is likely correct. If so, increased metals exposures may help explain massive recent increases in neurodegenerative diseases.

2. Materials and methods

2.1. Study design

To assess the neurodegeneration hypothesis, this article used a number of procedures to carry out this research. Although there are no widely agreed-upon procedures or study designs for reviews [70,71], this study proceeded on the basis of 5 key steps that many researchers say should be included in a review. These are (1) framing the question for review, (2) identifying relevant work, (3) assessing the quality of studies, (4) summarizing the evidence, and (5) interpreting the findings [72]. Procedure (1) has already been spelled out in section 1, especially 1.1.

Procedure (2) involved electronically scanning the Web of Science for all available, English-language resources on the topics of neurodegeneration and health effects of metals, then including those that were "most important." Authors judged articles as "most important" if they were among those that appear to provide the best or strongest empirical evidence for/against the neurodegeneration hypothesis. According to study-selection criteria, research could be either experimental, observational, or qualitative studies, although no important quantitative studies were omitted. Study-selection criteria also allowed not including studies whose specific results were incorporated into later research and thus improved upon by later studies.

Procedure (3), assessing the quality of studies relevant to the neurodegeneration hypothesis, involved logical and methodological analysis of each of the studies, relative to how well they satisfied classic norms for scientific assessment, such adequate sample size and study length, and how well they satisfied three main qualitative methods of causal assessment. These causal norms include (3.1) the mechanistic method, (3.2) the unification-coherence method, and (3.3) the experimental-counterfactual method. The main criteria for assessing whether article evidence met each of these three key causal norms, are whether the authors follow all relevant classic norms for scientific assessment, whether they make any false assumptions in collecting/assessing/evaluating data, and whether they draw any conclusions that lead to scientifically questionable empirical consequences.

The three causal-assessment methods used in procedure (3) in this review article—respectively, (1) mechanistic, (2) unification-coherence, and (3) experimental-counterfactual methods—are important and relevant because they correspond to the respective guidelines that the US Environmental Protection Agency (US-EPA) calls "most salient" for causal assessment [73,74]. These "most salient" assessment tools are biological plausibility (a large part of which is what we

call the mechanistic method), consistency and coherence (what we call the unification-coherence method), and experiment and strength of association (what we call the experimental-counterfactual method) that correspond, respectively, to this study's assessment methods (1), (2), and (3). In addition, this study's causal-assessment methods (1), (2), (3) are important, both because they include the assessment method (3) that Bradford Hill called the "strongest support" for a causal claim [75], and because they include the same methods (2) and (3) that dominate causal assessment by the UN's International Agency for Research on Cancer, IARC [76,77,78], namely, consistency—and experimental manipulation-strength.

This article's procedure (4), summarizing the evidence, followed four systematic steps. These are (4.1) outlining the causal methods, e.g., mechanistic to be used to assess each article; (4.2) assessing what each method and each article reveal about the neurodegeneration hypothesis, (4.3) assessing the quality of the experimental, observational, and qualitative evidence in each article, and (4.4) assessing all known scientific responses to the evidence for and against the neurodegeneration hypothesis. Procedure (5), interpreting the findings, followed three main steps. These are (5.1) determining whether the overall summary could be trusted, (5.2) assessing all known or likely objections to the summary, and (5.3) assessing possible grounds for bias in any of the studies [72].

In addition to classic scientific ways of evaluating all research relevant to the neurodegeneration hypothesis, the three main causal methods are central, namely the mechanistic, unification-coherence, and experimental-counterfactual methods. Before using these three methods to assess the hypothesis, consider each and what they require.

2.2. Three main methods of causal assessment

2.2.1. The mechanistic method

The method of looking for and assessing mechanisms, that support the neurodevelopment hypothesis or not, is a plausible way to access the neurodegeneration hypothesis because in many fields of science, including neurobiology, satisfactory explanations often require providing descriptions of mechanisms and modes of action. This is partly because pollution effects often are assessed biologically and medically, yet many areas of biology have few, if any, laws. As a result, mechanisms often take the place of laws. For instance, two of the mechanisms of biological evolution are natural selection and genetic drift. Regarding pollution, one of the mechanisms through which DDT or PCBs can cause preterm birth is through chemical stimulation of uterine-contraction frequency [79].

The mechanistic method of causal assessment presupposes that an entity acts as a cause when it behaves according to a mechanism, a series of activities of entities that include regular, organized processes that produce regular effects. Mechanisms thus show how set-up conditions and intermediate stages of processes produce termination conditions that produce some effect, such as neurodegeneration [80-90]. Thus, mechanisms, such as processes associated with neural-protein build-up P might explain why people experience neurodegenerative diseases such as AD. Apart from its practical utility in science, the mechanistic account of causality seems plausible in part because it can provide sufficient conditions to explain how and which regularities actually explain [91]. Of course, not all causes are understood well enough to have mechanistic explanations, rather than merely statistical ones. Nevertheless, when one can find mechanisms, then use them to reproduce the

cause and effect, one has good evidence for a causal relationship.

2.2.2. The unification-coherence method

Unificationist methods of assessing causality likewise are a plausible way to evaluate the neurodegeneration hypothesis because, as already mentioned, they rely on the Bradford-Hill, US-EPA, and IARC norms of consistency and coherence—or unification—with other data to assess causal hypotheses. Unificationist methods also make sense because they presuppose that one aim of science explanation is unification, comprehending a maximum of facts, regularities, or phenomena—such as scores of different neurodegenerative diseases and their symptoms—in terms of a minimum of theoretical concepts/assumptions [87,92]. One of the classic unifications in science is that of electricity and magnetism, now understood to be two aspects of the same causal phenomena, referred to as electromagnetism. According to unificationists, a set of sentences (allegedly explaining phenomena) is superior to other such sets, insofar as it unites many observations/phenomena under one cause by providing as few, stringent, and complete as possible, argument-patterns that can be used to derive the greatest number of different accepted claims [88,93-96].

In response to the objection that unificationist methods may incorrectly give primacy to unification, not explanation of scientific phenomena [97,98], it is important to note that unificationist methods require explanation of phenomena, not merely the simplicity and predictive power that unification brings. Thus their goal is not merely unifying arguments, phenomena, and regularities, but also unifying different explanations of different phenomena—as with the earlier electricity and magnetism example. This unification therefore requires finding the best explanation, one that uses no accidental generalizations.

2.2.3. Experimental-counterfactual methods

Experimental-counterfactual methods of assessing potential causal relationships likewise are plausible because they can provide answers to what-if-things-had-been-different questions that are at the heart of experimental science. That is, they can identify conditions, factors, and interventions that might be used to manipulate outcomes or effects. For these methods, successful causal explanations are expressed as counterfactuals that exhibit stable and invariant patterns of dependency between the cause/explanans/factor and the effect/explanandum/outcome. These patterns reveal how interventions produce changes in the cause that are systematically associated with changes in the effect. According to this method, better causal explanations have dependency patterns that are more detailed, accurate, and complete—regarding identifying all changes in all the factors and only the factors that, if changed by experiment, are associated with changes in the explanandum/outcome [99-103].

Many Bradford Hill, US-EPA, and IARC uses of "biological gradient" provide examples of using experimental-counterfactual methods to assess causality. For instance when one manipulates doses or exposures to some pollutant, then observes that higher doses are associated with greater effects, but lower doses with lesser effects, and the absence of exposures with no effects, one observes a biological gradient. This is a dose-response relationship that is experimentally manipulated and that takes account of counterfactual situations, such as the absence of exposure. This apparent dependency relationship between pollutant dose and biological harm is a key sign of a causal relationship, the very relationship that the experimental-counterfactual method attempts to discover.

2.3. The role of scientific consensus regarding the three causal-assessment methods

Another key reason that it makes sense to assess the neurodegeneration hypothesis by means of the three causal norms—that we call the mechanistic, unificationist-coherence, and experimental-counterfactual methods—is that these appear to be the norms on which the US-EPA relied, when it failed even to assess a possible causal relationship between metals exposures and neurodegenerative diseases. Thus, it is good to attempt to use the same methods, as those who fail to accept the neurodegeneration hypothesis, in order to evaluate all the evidence relevant to the hypothesis.

How do we know that these three causal methods (mechanistic, unificationist-coherence, and experimental-counterfactual), used in evaluating US smelter threats, were the basis for US-EPA's "failure to address the increased risks of neurodegenerative diseases caused by exposure to heavy metals, including increased risks of multiple sclerosis (known to have occurred at atypically high levels in [the former smelter at] DePue) and Alzheimer's disease, among others" [104]? We know this because US-EPA defends its failure by saying "there is not yet consensus regarding the causative agents" of excess neurodegenerative diseases at US smelter sites [8]. As a result, US-EPA has deliberately and officially declined to consider assessing the neurodegeneration hypothesis, even when asked to do so [8].

Moreover, when US-EPA says there is "no consensus" that metals exposure can cause neurodegenerative disease, it says it means there is "no weight-of-evidence" for the neurodegeneration hypothesis; it says it uses the phrases "no consensus" and "no weight of evidence" interchangeably [8]. But US-EPA's weight-of-evidence norms for causal assessment are precisely the causal-assessment methods (mechanistic, unificationist-coherence, and experimental-counterfactual) that we use here. As emphasized earlier in section 2.1, US-EPA says the 3 causal norms we use are the "most salient" in causal assessment, and both Hill and IARC causal analyses support this US-EPA position. In fact, US-EPA has specific requirements to assess causal claims about human harms—especially from pollutants—in terms of "weight of evidence" [73,74,105], or "preponderance of the information" [105].

Our use of the three causal-assessment methods (mechanistic, unificationist-coherence, and experimental-counterfactual), the "most salient" part of causal assessment, also is important because US-EPA explicitly rejects any other (than weight-of-evidence as just defined) criteria (such as consensus) for causal assessment. It says there are no other necessary or sufficient norms for causal assessment [73,74].

3. Results

3.1. What the three causal methods reveal about the neurodegeneration hypothesis

Thus, preceding sections reveal that our three key norms for causal assessment—the mechanist, unificationist-coherence, and experimental-counterfactual methods—are at least plausible. They also are mandated by US-EPA as the "most salient" causal norms, and they dominate both IARC and Hill strategies for causal assessment. As a result, it makes sense now to use these three methodological norms to assess the neurodegeneration hypothesis. Subsequent paragraphs evaluate this hypothesis via each of these three methods. These evaluations show that (1) the mechanist method supports the

neurodegeneration hypothesis for two main reasons. (1.1) Accepting this hypothesis is superior to not accepting it, (1.1) because accepting the hypothesis provides mechanisms to explain excess neurodegenerative diseases, whereas not accepting it does not, and (1.2) because accepting the hypothesis provides (whereas not accepting it does not) 3 mechanisms NOP whose operation is necessary for mild cognitive impairment and neurodegenerative diseases, including MS, AD, PD, and ALS.

Subsequent paragraphs likewise show that (2) the unificationist-coherence method supports the neurodegeneration hypothesis for two main reasons. Accepting this hypothesis is superior to not accepting it, (2.1) because accepting the hypothesis (but not not-accepting it) provides a unifying cause of excess neurodegenerative diseases, and (2.2) because not accepting the hypothesis (but not accepting it) ignores the fact that the hypothesis unifies similar neurodegenerative harms, from many different metals and metalloids, on many different populations, through many different exposure routes and scientific methods.

Finally, subsequent paragraphs likewise show that (3) the experimental-counterfactual method supports the neurodegeneration hypothesis for two main reasons. Accepting this hypothesis is superior to not accepting it, (3.1) because accepting the hypothesis (but not not-accepting it) provides reasons that support counterfactual inferences, to explain excess DePue and other smelter-site neurodegenerative diseases. Also, (3.2) those who fail to accept the hypothesis ignore the fact (while those who accept the hypothesis do not) that interventionist accounts support the hypothesis because animal-experimental studies clearly show that counterfactually manipulating animal exposures to metals, by varying doses, reveals a pattern showing that changing metals' doses (causes) changes neurological phenomena (effects). That is, metals-exposure levels are positively correlated with central-nervous-system levels of NOP, all 3 of which are necessary for developing mild cognitive impairment and neurodegenerative diseases. Moreover, as already noted, P is a "core biomarker" for neurodegeneration. Once metal nanoparticles enter the brain and cause NO, then P, increased brain levels of harmful oxidized proteins interfere with nerve transmission, even before they clump into plaque or tangles [106-109].

3.2. What the mechanistic method reveals about the neurodegeneration hypothesis

Consider first how one might evaluate the neurodegeneration hypothesis in terms of the mechanistic method. What insights does this method provide about the neurodegeneration hypothesis? Subsequent paragraphs argue that not accepting the hypothesis is questionable because it proposes no alternative mechanisms to explain increased neurodegenerative-disease rates in areas of high metals/metalloids exposure. Accepting the neurodegeneration hypothesis, however, satisfies the mechanistic method of causality insofar as NOP mechanisms, including core biomarker P, are necessary conditions for neurodegenerative diseases, including AD, ALS, MS, and PD to develop [20,27,35]. Thus, on the basis of the mechanistic method of assessing causality, accepting the neurodegeneration hypothesis appears superior to not accepting it.

3.2.1. Three mechanisms of metals-induced neurodegenerative harms

As discussed earlier, the NOP mechanisms, in terms of which neurodegenerative disease is defined, operate in terms of several related brain processes, including amyloid-beta processes and tau

processes. Each of these processes is tied to P, overproduction of different damaged/toxic brain proteins, such as amyloid-beta and tau in AD, and alpha-synuclein in PD. In the amyloid-beta process, for instance, P takes the form of overproducing damaged amyloid-beta. In the tau process, P takes the form of overproducing and overphosphorylating tau proteins. (Phosphorylation, the addition of a phosphate group to a protein, causes its enzymes to become activated/deactivated, such that protein dysfunction and misfolding occurs, and nerve transmission is damaged.)

The neurodegenerative mechanisms NOP, and the processes through which they operate, begin when a person inhales/ingests metals more quickly than can be excreted. Even metals with a biological role—such as cobalt, copper, iron, manganese, and zinc—may cause neurotoxicity by free-radical-mediated oxidative stress O and subsequent chronic neuroinflammation N, impairment of mitochondrial function, and P alteration of protein structure and overproduction of damaged proteins, the core biomarker of neurodegeneration [33,46]. When people inhale particulate metals that are fine/ultrafine (less than 2.4 micrometers in diameter), the metal particulates move up the nose, into the olfactory bulb, directly into the brain. When metals are ingested, the blood transports them to every part of the body, including the brain. Neurodegeneration occurs because the brain treats all metal particulates as "invaders" and induces NO, including swelling and massing of white blood cells to protect the brain and immobilize the metal particles. Once NO cause P, the biomarker of neurodegeneration, however, P produces even more NO, killing and damaging neurons and blocking brain-cell signaling, in a worsening, repeated, chronic cycle of NOP, NOP, NOP.

In the amyloid-beta process, metal ions, including copper, iron, and zinc, bind to amyloid-beta, increasing brain levels of this toxic protein [110,111]. The metals-mediated, toxic-amyloid-beta process, involving mechanisms NOP, involves a self-reinforcing cycle of neuroinflammation (N), neurodegeneration through OP, and further, chronic N neuroinflammation, in a cycle of NOP, NOP, NOP [52]:

Metal/metalloid particles enter brain → neuroinflammation/swelling/white blood cell massing occur (N) → metals bind to some amyloid-beta proteins, making them toxic, and elevating their levels (P) → free radicals are produced, oxidative stress in the brain (O) → neuroinflammation increases (N) and becomes chronic (N), in a recurrent and chronic neurodegenerative NPO cycle [45,50,106,112-118].

The hyperphosphorylation-mediated, toxic-tau process, also involving mechanisms NOP, likewise involves a self-reinforcing and cycle of neuroinflammation (N), neurodegeneration through O and P , and further NOP, NOP, NOP:

Metal/metalloid particles enter brain → neuroinflammation/swelling/white blood cell massing occurs (N) → hyperphosphorylation damages tau-proteins in the brain and elevates their levels (P) → causing reactive oxygen species, oxidative stress (O), brain-cell damage/death and reduced nerve transmission → neuroinflammation (N) increases and become chronic → hyperphosphorylation increases, and so on, in a repeated, neurodegenerative cycle of NOP, NOP, NOP. [18,50,106,112,113,115,116,117,119].

Although scientists know that accumulation of neurofibrillary tangles or plaques do not themselves cause neurodegenerative disease but instead are effects, the tangles or plaques also promote N and the neurodegenerative NOP cycle [52]. Thus metals/metalloid exposure induces the repeated NOP cycle of mechanisms, including the core neurodegeneration biomarker P [18,45,46,50,52,106,112-117,119].

3.2.2. Animal-experiment evidence for NOP mechanisms

Given the preceding examples of NOP mechanisms, consider six of the hundreds of animal studies showing that metals-exposure induces NOP mechanisms, including the core neurodegeneration-biomarker P, and the processes in which NOP occur. One study on rats showed that arsenic exposure induces protein tau hyperphosphorylation and over-transcription of the gene encoding the amyloid-precursor protein, thus producing the hallmark neuropathologic feature P of AD [19]. A study on mice showed that copper induces P, the phosphorylation and aggregation of tau proteins [27]. Another study showed mercury exposure increases P, toxic beta-amyloid production and hyperphosphorylation of tau protein in rats [52]. A fourth study on rats confirmed that cobalt increases P, toxic beta-amyloid production by upregulating expression of beta-amyloid precursor proteins [27]. A fifth study on rats showed mercury and silver at blood concentrations of 0.33 mM cause brain-cell death, then N and all its outcomes [32]. A fifth experimental study on monkeys showed that manganese exposure caused the rats to develop P, beta-amyloid increases and resulting plaque when they were only about 6-8 years old; these results show metals such as manganese cause early AD [22], just as they do in human children [50,120,121].

Because studies on human AD victims show no association between age and brain-metals levels, between controls and AD patients [121], age alone likely does not cause AD. Another factor, such as metals exposure, probably plays a significant role in AD. The sporadic or nongenetic/nonfamilial nature of 90–95 percent of AD cases also strongly suggests that environmental factors like metals play significant roles in its pathogenesis [122].

3.2.3. Responses to these mechanistic arguments for the neurodegeneration hypothesis

In response to preceding animal-experimental/human-observational evidence for NOP and C, and thus for mechanistic evidence for the neurodegeneration hypothesis, those who fail to accept this hypothesis might question whether N is a genuine mechanism of neurodegeneration. After all, N does not always cause disease. Yet if a mechanism always works in the same way under the same conditions, objectors say the N mechanism should always cause disease [123]. They note that N does not always work in the same way because it is often beneficial, eliminating pathogens, clearing brain debris, and aiding repair [124]. Besides, in the case of MS, they claim neurodegeneration may occur independently of N, because very little N is seen in cortical MS plaques, as evidenced by the fact that anti-inflammatory drugs often have little/no effect on the disease [123]. Thus if N is (a) often beneficial, not neurodegenerative, and (b) not present in all neurodegenerative diseases, those who fail to accept the neurodegeneration hypothesis may have grounds to doubt mechanistic support for the hypothesis.

However, those who fail to accept the neurodegeneration hypothesis err regarding (a). Although N does not always cause neurodegenerative disease, there are two types of neuroinflammation, acute and chronic. Acute inflammation is the sequence of tissue-responses that occurs within the first few hours after injury and is resolved when invaders are killed/removed [125]. Chronic N is what occurs after the first few hours of exposure, and invaders are not killed/removed [125]. In chronic N, microglia (the brain's immune cells) and inflammatory cells are activated and release pro-inflammatory cytokines [124]. Although chronic N always causes neurodegenerative diseases, including MS, AD, PD, and ALS [18,25,45,50,52,106,112-117,119], acute/several-hours-long N can

be beneficial. When microglia detect pathogens/toxins/damage, they initially cause acute N to help clear the threat. However, if the problem is not quickly resolved, signal cascades result in the expression of new/toxic brain proteins P, and microglia become chronically activated, releasing pro-inflammatory cytokines and O. Continued N and presence of the pathogen/toxin/damage, and chronic release of cytokines and O, causes chronic N [124], chronic NOP that kills more and more neurons, one of the defining characteristics of neurodegenerative disease [124,126]. Because the objection confuses chronic and acute N and yet provides no alternative mechanisms to prevent NOP, it seems reasonable to support the neurodegeneration hypothesis over not accepting it.

Likewise, those who fail to accept the neurodegeneration hypothesis also err regarding (b), as they claim that N does not always characterize neurodegenerative disease, as anti-inflammatory drugs often fail to address such disease. However, (b) errs because in progressive neurodegenerative disease, such as MS, N often becomes trapped behind a closed/repaired blood-brain barrier, where anti-inflammatory treatments cannot not reach this N and address it [123]. Thus, the purported drug evidence does not show absence of N in neurodegenerative disease. Besides, earlier evidence showed that another mechanism/biomarker of neurodegeneration, P, causes/results from N; hence it is reasonable to reject this objection and to prefer the neurodegeneration hypothesis over not accepting it. Again, those who fail to accept the hypothesis provide no alternative mechanisms either that induce neurodegenerative diseases, in the face of metals exposures, or that would block the action of metals-caused mechanisms NOP. Hence, the mechanistic method suggests weight-of-evidence lies with the neurodegeneration hypothesis, not with those who fail to accept it. What about the two other main methods of causally assessing hypotheses?

3.3. What the unificationist method reveals about the neurodegeneration hypothesis

Specifically, what about the unificationist account? Would it support the neurodegeneration hypothesis or not? This section shows that the hypothesis unifies diverse neurological phenomena in at least 5 ways, whereas not accepting it achieves no theoretical/empirical unification. That is, accepting the neurodegeneration hypothesis unifies (1) the harmful neurological and neurodegenerative effects (2) of many different metals/metalloids, (3) on many different populations, (4) revealed through several different scientific methods, and (5) documented via many different exposure routes. Consider (1).

3.3.1. The neurodegeneration hypothesis unifies harms from many metals

Unificationist methods of assessing causality support the neurodegeneration hypothesis because it unifies the same three neurodegenerative effects, NOP, all of which are associated with metals/metalloid exposure, including arsenic, cadmium, cobalt, copper, iron, lead, manganese, mercury, silver, sodium, vanadium, and zinc—whereas failure to accept this hypothesis achieves no unification. Scientists agree that NOP are necessary for mild cognitive impairment and neurodegenerative disease and that P is a core biomarker of neurodegeneration [15-22,25-33,35,37,38,46,106-109]. N and O may occur briefly/non-chronically and in tiny areas of the brain, in the absence of neurodegenerative diseases, but neurodegenerative diseases never occur without chronic NOP, and P is the key biomarker of such disease. For instance,

- N appears after any exposure (via food/water/air/soil/skin) whatsoever to arsenic [19] or

mercury [52], neither of which has a safe dose [51]. Daily drinking-water exposures, with levels as low as 8 μM copper [17,127]; 60 ppm iron [25,26,35]; or 14.5 μg/L zinc all trigger N [17,121].

• P appears after any exposure (via food/water/air/soil/skin) whatsoever to arsenic [19], lead [20,21,28], or mercury [52], none of which has a safe dose [51]. Daily exposures as low as 0.13 μg cobalt/L water [27,128,129]; 0.01498 mmol copper/L blood serum [27,31]; 3.3–10 ppm manganese/blood [22,37]; 7.7 mmol/L sodium in cerebrospinal fluid [38,130]; or 14.5 μg/L zinc in cerebrospinal fluid, all trigger P [15,17,121].

• O appears after any exposure (via food/water/air/soil/skin) whatsoever to arsenic [19,30], cadmium [16,27], mercury [18,32,52], silver [32], or vanadium [29], none of which has a safe dose [51]. Daily exposures to drinking water, with levels as low as 0.13 μg/L cobalt [27,129]; 8 μM copper [27,127]; 60 ppm iron [18,25,35]; or 12.82 ppm airborne manganese all trigger O and resulting neuron death/damage [18,39].

Those who fail to accept the neurodegeneration hypothesis, however, deny that the hypothesis unifies neurodegenerative effects NOP across many metals. They take this position because human-study results often are inconsistent [131-135]. For instance, although classic-literature-review articles on metals and neurodegenerative disease, especially AD, indicate that all animal-/in-vitro experiments consistently show metals induce greater cognitive impairment and "all pathological changes" found in neurodegenerative diseases such as AD, those who doubt the neurodegeneration hypothesis say human-observational results are inconsistent. They say that (a) subjects' metals levels in blood/cerebrospinal fluid/hair/nails/urine are not always consistent with their neurodegenerative status, e.g., AD severity. They also claim that (b) without multiple-decades-long, cohort studies that provide dose-response numbers for metals-neurodegeneration, there is no good causal evidence that mild cognitive impairments, from low-level-metals exposure, has some probability of becoming neurodegenerative disease [52,136].

However, the preceding objections to the neurodegeneration hypothesis are suspect on several grounds. At least 4 reasons suggest (a) is questionable. First, interpersonal variations in genetics/immunity/metals excretion/so on, can account for different neurodegenerative-disease levels, given similar metals levels. Second, as already argued, neurodegenerative status is proportional to P, not metals levels. Third, it is wrong to claim that results of different observational studies, using different populations/methods/data, are inconsistent, because the different populations/methods/data in observational studies could explain the differences. Besides, the different studies do not affirm/deny the same thing in the same respect, so they cannot be inconsistent. Fourth, because all the carefully controlled animal-/in-vitro-experimental data consistently support the neurodegeneration hypothesis, there is little reason to doubt it, just because observational studies supposedly are inconsistent. There is no reason that flawed and superior studies should have consistent results. For instance, the objectors themselves note that some human studies (correctly) used glass, while others (incorrectly) used plastic, test tubes for blood samples. Yet the latter allows more volatilization/vaporization of metals such as cadmium, mercury, zinc, thus lower recorded "doses" [52]. Therefore, rather than challenging the neurodegeneration hypothesis, the supposed inconsistences in human-observational studies likely result not from the hypothesis's being wrong, but from poor methods. These poor methods include not controlling for confounders, or ignoring different metals-absorption or detoxification capacities of different people/populations.

Part (b) of this objection to the neurodegeneration hypothesis likewise is questionable because although the objection demands it, it is usually impossible to derive a quantitative dose-response

curve from purely human-observational data. This is because one has no randomized/experimental data for humans and cannot fully control for confounders. Yet human-dosing experiments with metals are ethically/legally prohibited. This is why US-EPA says "there is frequently a lack of dose-response data available for human subjects" [137]. Moreover because weight-of-evidence assessments always presuppose a particular assessment time, assessment judgments ought not be deferred merely because multiple-decades-long cohort studies have not been done. Therefore, the best-available data, at present, argue for the neurodegeneration hypothesis over not accepting it, because it unifies the same NOP effects from diverse metals.

3.3.2. The neurodegeneration hypothesis unifies many diseases

Unificationist methods of causal assessment also support the neurodegeneration hypothesis because not accepting it unifies no neurodegenerative phenomena across many metals-exposed populations. However, the hypothesis unifies increased neurodegenerative diseases (such as MS, AD, PD, and ALS, including their 3 necessary conditions NOP and their core biomarker P, with increased metals exposures), across at least 4 diverse populations, including animal, residential, worker, and pre-natal groups [11,34,36].

When animals and humans populations face metals exposures, both experience NOP [106-109]. For instance, mice and rats, exposed to copper or iron, exhibit increased N [17,35]. Rats or other rodents, exposed to arsenic [30], cadmium [16], mercury [32], silver [32], or vanadium [29], exhibit O. And when primates [22,37], rodents [30], mice [17,20,21], and rats [52], respectively, are exposed to manganese, arsenic, lead or zinc, or mercury, they exhibit P, all of which suggest there are regular patterns of neurodegenerative effects, caused by the same mechanisms NOP, identified by the same core biomarker P [46], across different animal populations.

In response to this defense of the neurodegeneration hypothesis by unifying animal populations though NOP mechanisms, opponents often reject animal studies as a basis for extrapolating about human harm [138,139,140]. For example, when some scientists analyzed lead-exposure effects, they concluded that ignorance about different species' physiological, toxicokinetics, and metals-dynamics differences makes extrapolation to other species difficult [138].

However, rejecting animal studies and therefore failing to accept the neurodegeneration hypothesis, is questionable because animal-experiment studies can be, and almost always are, used to draw conclusions about humans; this is typically because the animal studies are experimental, and the human studies are not [141,142,143]. Although extrapolations from animals to humans may have some imprecision, as long as scientists use appropriate animal models, they make reasonable predictions about effects on humans. Those who object to animal extrapolation also overestimate difficulties with getting accurate animal-exposure data, yet underestimate difficulties with getting accurate human-exposure data. After all, animal experiments rely on (1) intended, controlled exposures; (2) direct, large-sample observation of exposures to thousands of subjects; (3) long-term observation of exposures that capture lifetime or multiple-generation effects; (4) consistent or constant exposures over time, and (5) empirically-confirmed exposures obtained through frequent measurements of differences between target-exposures and actual delivered doses.

In contrast, human-observational studies typically rely on (1') unintended exposures; (2') indirect, uncontrolled, small-sample observations of ten to hundreds of subjects; (3') short-term observations, susceptible to confounding, bias, missing/underestimating effects, ignoring

inter-individual variability, and ignoring latent harms; (4') variable exposures, and (5') estimated, after-the-fact exposures, given ethical/legal problems with human experiments involving harmful exposures. For both sets of all 5 reasons, human-observational studies usually have greater exposure-related uncertainties and less ability to control quality and thus produce good science, than do animal-experimental studies [144]. Besides, if those who fail to accept the neurodegeneration hypothesis, do so because they reject animal-to-human extrapolation regarding metals, they also would have to reject any animal studies showing no metals-related neurological harm (if such studies existed), as well as most cancer studies. Rejecting animal-to-human extrapolation also fails provide grounds for not accepting the neurodegeneration hypothesis because, as subsequent paragraphs reveal, support for this hypothesis is not limited to animal-experiment studies but includes human-observational studies that confirm similar results, namely human-animal neurodegeneration from metals. Hence this animal objection fails.

Regarding human data that support the neurodegeneration hypothesis, many adult-residential populations reveal metals' neurodegenerative effects. Consider 4 of thousands of different human-epidemiological studies [11,34,36,145] that support the neurodegeneration hypothesis, especially regarding MS. First, a 1971–1990 study showed that "a significant excess" of MS cases, 10 times above normal, occurred in DePue, Illinois, where residents had "significant exposure" to many metals, including zinc [11]. Second, a Taiwan study showed that ingesting food grown in lead-contaminated (5.3 mg/kg) soil is "positively correlated with" MS incidence [34]. Third, multiple-location European studies have shown a "significant positive correlation" between higher soil-barium levels and higher MS incidence [36]. Because these MS increases have been so steep and rapid, scientists say genetics alone cannot explain them, and heavy metals are the likely culprit [36]. Fourth, another US study, comparing 29 million Medicare beneficiaries, showed that counties with higher manganese releases from smelters and industrial facilities had "significantly elevated" PD risks [145].

Regarding adult-worker populations, hundreds of other studies also support the neurodegeneration hypothesis because they tie higher metals' exposures to higher rates of neurodegenerative disease. For instance, smelter workers and welders who are exposed to workplace manganese have higher rates of PD [23,39,146]. Battery-factory workers, exposed to occupational nickel and cadmium, suffer higher rates of brain atrophy and ALS syndromes [13,147,148].

In response, those who fail to accept the neurodegeneration hypothesis object to the adult-residential and adult-worker arguments by pointing to shortcomings in the preceding human-epidemiological studies supporting the hypothesis. For instance, one study found a "poor correlation" between blood-manganese levels and smelter-employment duration, although PD incidence was positively correlated with blood-manganese levels [39]. This objection, however, errs for at least two reasons. The most obvious reason is that there are no grounds to assume that blood-metals levels are correlated with length of employment, given different exposures at different jobs within the smelter, and given inter-individual differences in genetics, absorption, and detoxification. This objection to the neurodegeneration hypothesis also fails for some of the same reasons that the earlier "inconsistency" objection errs. It points to flaws in the observational data supporting the neurodegeneration hypothesis, flaws often unavoidable in non-experimental studies. Yet it ignores the preceding animal-experiment data that support the neurodegeneration hypothesis, including studies showing that virtually all metals induce three necessary conditions (NOP) for MS, AD, PD, ALS, and so on [15-22,25-32,34,35,37,38]. Thus weight-of-evidence considerations support

the neurodegeneration hypothesis, rather than this objection.

Evidence from pre-natal populations likewise supports the neurodegeneration hypothesis, according to unificationist methods, because children with prenatal-metals exposures have increased incidence of harmful neurodevelopmental effects, ranging from ADHD and lowered IQ, to cognitive deficits in attention, memory, language, and visuospatial skills [12,40]. Moreover, these neurodevelopmental harms exist forever and may worsen, as neurodegenerative disease does. For example, children with blood-lead levels greater than 2 μg/dL—only 20 percent of US-EPA's allowed blood-lead levels—are at a 4.1-fold increased risk of ADHD [14,149]. The estimated IQ decrement associated with an increase in blood-lead levels from 2.4 to 10 μg/dL is approximately 4 points (95% CI, 2.4–5.3) [24]. Overall, exposure to lead alone causes a loss of 22,947,40 IQ points/year, just for US children ages 0-5, a neurodevelopmental loss causing future-income losses of roughly $319 billion/year in the US [150]. This occurs mainly because developing brains are uniquely susceptible to neurotoxins, such as metals, that alter the neurotransmitter levels needed both for prenatal brain development and for avoiding adult neurodegeneration, such as AD [28,151]. Because prenatal metals exposures cause permanent cognitive declines in children similar to the permanent declines found in adult neurodegenerative disease, and because both occur through similar metals damage to protein neurotransmitters, the neurodegeneration hypothesis provides a way to unify these prenatal and adult harms from metals.

In response, those who fail to accept the neurodegeneration hypothesis point to shortcomings in prenatal-observational studies. In general, they can always cite some proposed confounders that could negate the neurodegeneration hypothesis and provide non-metals explanations of neurodegeneration, such as failure to control for a nonrandom assortment of genetic risk factors [11]. For instance, those who fail to accept the neurodegeneration hypothesis often point to questions about specific studies, claiming that neurodegenerative harms, allegedly caused by prenatal metals, could have been caused by confounders such as maternal exposure to cigarettes/alcohol/polychlorinated biphenyls or PCBs, given that observational studies cannot control for all confounders [40].

The preceding "confounder" objection against the neurodegeneration hypothesis errs, however, because the issue is not the obvious methodological weakness of all human-observational studies, namely, that they can neither control for all confounders nor randomize subjects/treatments. This is not the issue because, as the response to the earlier consistency objection noted, ethics/law requires using only observational/non-experimental metals studies on humans. This fact that explains why epidemiological studies are the foundation of virtually all public-health science [152]. Thus the issue is whether the strongest/largest/best-controlled human-epidemiological studies support accepting or not accepting the neurodegeneration hypothesis [153]. The issue whether the weight-of-evidence supports accepting or not accepting the neurodegeneration hypothesis.

Moreover, although the confounder objection attributes prenatal neurodegenerative effects to PCBs/alcohol/tobacco exposure, not to metals [40], the study itself rules out these alleged confounders. Although PCBs were "weakly associated" with neuropsychological deficits and memory problems in this study, because PCBs were not associated with metals exposures, they could not have caused confounding. Similarly, although maternal smoking and alcohol drinking during pregnancy are positively associated with some of the same adverse neuropsychological outcomes linked to metals exposure [40], they also are unlikely confounders because the study showed that adverse lead effects remained the same, regardless of whether or not maternal tobacco/alcohol use

occurred during pregnancy [40]. Thus the confounder objection to the unificationist case for accepting the neurodegeneration hypothesis fails, and those who fail to accept the hypothesis have provided no alternative way to unify neurodegenerative harms across 4 different populations. Therefore, on grounds of experimental and observational studies on 4 different types of populations, accepting the neurodegeneration hypothesis appears more plausible than not accepting it, partly because the hypothesis-supporting studies appear to use no accidental generalizations that would weaken the unification [154].

3.3.3. The neurodegeneration hypothesis unifies many ways of showing neurodegeneration

Unificationist methods of assessing causality also support accepting the neurodegeneration hypothesis over not accepting it because the latter unifies no diverse scientific methods, all of which provide evidence against metals-induced neurodegenerative disease. However, accepting the neurodegeneration hypothesis does achieve unification. More specifically, it unifies at least two different scientific methods, animal-experimental and human-observational studies, both of which show that not accepting the hypothesis is questionable, and that three necessary conditions NOP for neurodegenerative disease, including the core biomarker of neurodegeneration, P, are associated with metals exposure. Thus both animal-experimental methods [16,17,20,21,22,29,30,32,35,37,52], and human-observational methods [11,12,23,28,34,36,39,40,147] support accepting the neurodegeneration hypothesis.

Interestingly, the neurodegeneration hypothesis also unites, while failure to accept it does not, the experimental and observational methods of theoretical science with the more practical strategies of medical treatment. Many physicians and pharmacologists have discovered that they can ameliorate neurodegenerative problems by reducing brain levels of metals through chelation [155,156,157]. Theoretical scientists likewise say that because disrupted metal homeostasis is a consistent feature of all neurodegenerative disease, therapy should target these metals [158-161]. The success of metals-removing chelation in ameliorating neurodegeneration suggests that, on a practical level, increasing brain levels of metals could exacerbate if not cause neurodegeneration, just as proponents of the neurodegeneration hypothesis claim. Thus this hypothesis appears to unify both diverse scientific methods—and the methods of science and medical treatment. In contrast, not accepting the hypothesis unifies no metals, populations, or methods. Thus, it seems reasonable to accept the neurodegeneration hypothesis.

3.3.4. The neurodegeneration hypothesis unifies many exposure routes

Accepting the neurodegeneration hypothesis likewise unifies evidence of neurodegenerative harm from multiple metals-exposure routes. Numerous studies show that classic NOP conditions, necessary for neurodegenerative diseases such as AD and PD, result from metal/metalloid exposure via food/water/air/soil/skin. These exposures occur through inhaling nano metal/metalloid particles from auto exhaust and windblown soil [11,12], ingesting food grown in metals-contaminated water/soil [34], or skin absorption of metals-contaminated water/soil [36]. However, because those, who fail to accept this hypothesis, list no exposure routes through which people remain invulnerable to metals' harm, they cannot unify these routes. However, the neurodegeneration hypothesis unifies a variety of exposure routes and explains increased population rates of neurodegenerative diseases

such as MS [11,12,34,36].

Previous arguments show that because accepting the neurodegeneration hypothesis (but not failure to accept it) can unify effects of diverse metals, on diverse populations, via diverse scientific methods and exposure routes, it is more likely than not that metal/metalloid exposures—unified in all these ways—can produce neurodegenerative diseases. This unification argues for accepting the neurodegeneration hypothesis over not accepting. The main reason is that, as the unificationist account of causality requires, different evidence/populations/methods establish the same pattern (increased incidence of harmful symptoms resulting in neurodegenerative diseases) in many different cases (diverse metals/populations/scientific methods/exposure routes). On the other hand, not accepting the hypothesis offers no such unification. Instead, failure to accept this hypothesis merely arises because critics note some imperfection/uncertainty in the neurodegeneration hypothesis, although they have neither evidence that the uncertainty affects the hypothesis, nor some alternative hypothesis that better unifies the many manifestations of the metals-neurodegeneration link. Therefore, unificationist methods of assessing causality suggest that it is more reasonable to accept the neurodegeneration hypothesis than not to accept it. But what does the last of the three causal-assessment methods, the experimental-counterfactual method, say about the neurodegeneration hypothesis?

3.4. What the experimental-counterfactual method reveals about neurodegeneration

The experimental-counterfactual method also offers many insights about the neurodegeneration hypothesis because it requires no scientific laws, and biology has few genuine laws. Yet, although many biological generalizations are less stable than physical/chemical laws, as experimentalists note, it is important to know the conditions under which biological generalizations are not stable. Such stability patterns can reveal valuable biological information about the contingency, insensitivity, and invariance of causal relationships [99,100,162,163], even when there may be no laws.

Despite the dearth of neurobiological laws, using the experimental-counterfactual method can support the neurodegeneration hypothesis because it can help explain that the hypothesis is invariant/stable/robust under experimental interventions and a wide range of conditions—because only then does the hypothesis support counterfactuals. Thus if one can manipulate metals (causes) so as to produce patterns of regular and varied neurodegenerative effects, then one has explained the causal relationship in the neurodegeneration hypothesis because one can control it. And as Woodward [99,164] confirms, it does not matter whether the manipulation can be carried out, only that the explanatory relationship describes what would happen if it were carried out. This is an important detail because many neurobiological patterns must rely partly on observational, not experimental, studies.

Do those who accept or those who fail to accept the neurodegeneration hypothesis do a better job of showing that they can experimentally control relevant causal relationships? This section of the article shows that not accepting the neurodegeneration hypothesis is questionable on grounds of the experimental-counterfactual account. Both human-observational and animal-experimental studies—that assess behavior under counterfactual conditions—support the neurodegeneration hypothesis. Consider first the experimental evidence.

3.4.1. Experimental-counterfactual support for metals-caused neurodegeneration

Animal experiments, that manipulate environments, show that experimental-counterfactual accounts support the neurodegeneration hypothesis. Experimentally exposing animals to metals/metalloids causes both chronic NOP, necessary conditions for neurodegenerative diseases such as MS, AD, PD, and ALS to develop, and the core biomarker P of neurodegenerative disease [20,27,35,46]. For instance, rats exposed to drinking water contaminated with arsenic (57.3 ppm) exhibit NO [30]. Rats injected with 27 ppm lead exhibit P, amyloid-beta increases 103–108 percent higher than unexposed controls [21]. Rats dosed with iron exhibit chronic N, and as N increases, brain-cell iron levels double or triple, worsening N and inducing O, in a vicious cycle [35]. Moreover experiments show that when brain cells of rats and mice exhibit P, amyloid-beta increases, this P increases brain-sodium levels two- to three-fold which, in turn increases N and O [38]. In short, hundreds of animal experiments show that increasing metals exposures raises NOP as compared to controls, and that as N increases, so do brain levels of metals such as iron, sodium, and zinc; this indicates that at least some metals bind to proteins such as amyloid-beta [15], further reinforcing the NOP cycle, and worsening neurodegeneration. In contrast, those who fail to accept the neurodegeneration hypothesis can point to no animal experiments showing that as metals exposure increases, NOP does not. Experimental-counterfactual support, in terms of animal experiments, thus argues for neurodegeneration hypothesis.

Human-observational studies also show that the experimental-counterfactual method supports the neurodegeneration hypothesis, through various "natural experiments." Based on manipulation or counterfactual circumstances regarding metal/metalloid exposure, these "natural experiments" show that controlling metals exposures can control neurological effects. For instance, before repair of one workplace, metals-smelter-ventilation system, airborne-manganese averaged > 12.82 ppm, worker-blood-manganese levels were up to 405 μg/L, and PD-incidence rates were 75 percent of smelter workers. After repair, airborne-manganese averaged < 1.96 ppm, worker-blood-manganese levels averaged 14.9 μg/L, and PD incidence was 0 [39]. Even without an experiment, the smelter-worker data show that increases/decreases in metals exposure increases/decreases blood-metals levels which, in turn, cause PD increases/decreases. Certainly, therefore, accepting the neurodegeneration hypothesis seems more plausible than not accepting it, as the latter would predict neither increased PD when metals levels rose nor reduced PD when metals levels fell.

3.4.2. An objection to experimental-counterfactual support for neurodegeneration

In response to experimental-counterfactual support for the neurodegeneration hypothesis, those who fail to accept this hypothesis might reject such natural experiments on the grounds that several large observational studies have failed to find any metals-neurodegenerative-disease correlation, such as between being a welder and incurring higher risks of PD [165,166,167]. However, the apparent failure of some studies to reveal a welding-and-PD association can be explained by the fact that all of these no-association studies err in 3–5 ways [165,166,167]. They fail to measure metals doses or blood-metals levels, to distinguish different levels of welding ventilation, to distinguish different jobs/exposures among welders, to control for the healthy-worker effect, or to control for confounders [168]. Virtually universally, these no-association welder studies ignore confounders, although the best observational studies do not. To take account of PD confounders, studies would need to control for

pesticide, solvent, and vehicle/highway-exhaust exposures, as all these factors are well known causes of PD. Instead, the flawed, no-association studies, cited by those who do not accept the neurodegeneration hypothesis, merely correlated public data on PD incidence among those whose occupations were listed as welders. However, when studies take account of dose, confounders, ventilation, and so on, all other things being equal, they reveal a dose-response curve for metals-PD, and they show welders have 10–16 times the incidence of PD as nonwelders [169,170,171]—both causal desiderata for experimental-counterfactual methods. As a result, accepting the neurodegeneration hypothesis seems more plausible than not accepting it, at least on experimental-counterfactual ground.

4. Discussion

4.1. What the results suggest

In sum, preceding paragraphs show that three key causal-assessment methods (mechanistic, unificationist-coherence, and experimental-counterfactual) provide human-observational and animal-experiment evidence that metals can induce the necessary NOP mechanisms of neurodegeneration, including the core biomarker P [16,17,20,21,22,29,30,32,35,37,52]—also unify all relevant populations, exposures and methods related to neurodegeneration, and finally experimentally and counterfactually show that accepting the neurodegeneration hypothesis seems more reasonable than not accepting it. Are these results reliable?

Several reasons suggest that the results, supporting the neurodegeneration hypothesis, are reliable because most of the relevant pro-hypothesis studies experimentally vary metal/metalloid exposures and reveal proportionate NOP effects. Yet those, who fail to accept the neurodegeneration hypothesis, have never controlled for confounders, measured dose, and so on, and yet revealed (i) the presence of a non-metals *mechanism* to explain neurodegenerative harms attributed to metals, (ii) unified reasons for the supposed absence of a metals-neurodegeneration relationship, and (iii) an account of alternative experiments/manipulations that explain increased neurodegeneration, amid increased metals exposures. For all these reasons, weight-of-evidence considerations (mechanistic, unificationist-coherence, and experimental-counterfactual methods) argue for accepting the neurodegeneration hypothesis, rather than for not accepting it and these arguments appear reliable.

The preceding results, in favor of accepting the neurodegeneration hypothesis, also appear reliable or trustworthy because this analysis has taken account of all important known objections to accepting the neurodegeneration hypothesis—and has answered them. In particular, the analysis and review has answered the objections in terms of specific details of each of the studies, such as supposed inconsistent results; studies that fail to measure dose/exposure; studies that fail to take account of experimental conditions, such metals-smelter ventilation; and studies that fail to control for confounders.

4.2. Possible additional objections to study results

However, in response to the preceding assessment showing that the mechanist, unificationist-coherence, and experimental-counterfactual accounts suggest that accepting the neurodegeneration hypothesis is more defensible than not accepting it, someone might have

additional objections, on at least four grounds, respectively, (1) hormesis, (2) human data, (3) specificity, and (4) competitors. These four objections might be formulated as questions, each of which we shall answer. (1) Although high-dose toxins/carcinogens have damaging effects, aren't low-dose toxins/carcinogens often either beneficial or not harmful? (2) Although hypothesis-comparison supports the neurodegeneration hypothesis, doesn't it remain questionable, to some degree, insofar as no human-dosing experiments support it? (3) Doesn't the neurodegeneration hypothesis have what Bradford Hill might call a specificity problem, insofar as neurodegenerative disease has more than one cause, and metals obviously cause many harms, apart from neurodegenerative ones? (4) Why should one accept the neurodegeneration hypothesis, if there are no competitor hypotheses against which to compare it? Won't any hypothesis with some explanatory power, such as the neurodegeneration hypothesis, always win over hypotheses that fail to accept some hypothesis? If so, why is the preceding analysis important? Consider each of these objections in order.

Objection (1), the hormesis objection, is that some scientists, mostly funded by industry, do not accept the neurodegeneration hypothesis because of supposed hormetic or beneficial effects of low-dose toxins on at least one biological endpoint [54-57]. Biological endpoints include hundreds of things, from cancer, to fingernail growth, to skin-coloration changes. However, virtually all scientists and the US National Academies of Sciences [172], say that net or all-endpoint effects of toxins are never beneficial, even at low doses. If so, hormesis proponents err in assuming they can use only one or several endpoints to assess hormesis, partly because while single/several endpoints may show beneficial effects, such effects are always trivial, in comparison to net or overall effects that are always negative for toxins/carcinogens. Another problem is that any alleged hormetic responses to toxins have high metabolic costs because they force the body to mount defenses to invaders/harms/toxins. If so, hormesis proponents err in assuming they can ignore the metabolic costs involved in the body's defending itself against toxins/harms because even allegedly beneficial, single-endpoint hormesis may have metabolic costs that may outweigh supposed benefits. Hence because net-endpoint effects of low-dose toxins are always extremely harmful, net-endpoint hormesis does not exist. Because single-endpoint hormesis is at best beneficial only in some trivial way, it is irrelevant to scientific/regulatory decisions about net-endpoint or overall harm. Hence no hormesis concept is both scientifically true and relevant. Single-endpoint hormesis is true but irrelevant because one needs to know net-endpoint effects. Net-endpoint hormesis is relevant but false, given that net effects of toxins are never beneficial. Thus, hormesis may appear plausible, but only because proponents equivocate about single, versus net, endpoint hormesis [173,174,175].

In addition, even hormesis proponents admit that supposed hormetic effects occur only from non-genotoxic hazards; hence they err in assuming they can generalize about hormesis when even they admit that supposed hormetic effects do not occur with genotoxic hazards. In fact, their only supposed metals-example of hormetic effects is unsubstantiated "reports" of selenium benefits [56]. Yet because virtually all metals can be genotoxic, alter patterns of gene expression, interfere with genes that suppress tumor growth, stimulate cell proliferation, and inhibit repair of damaged DNA, supposed hormetic effects are even less plausible for metals [53,176,177].

Objection (2) to accepting the neurodegeneration hypothesis is correct insofar as the absence of human-experimental evidence renders the hypothesis somewhat questionable. However, the demand for human-experimental/dosing evidence of human harm is misplaced for two reasons, already noted. First, obtaining such evidence typically is unethical/illegal, so its absence need not count against the

neurodegeneration hypothesis. Second, hypothesis-acceptance in neurobiological-epidemiological controversies ought to be less epistemically demanding than in purer science, insofar as the consequences of being wrong in epidemiology could risk great human-health harms, such as neurodevelopmental disease in children. In epidemiology, arguably one often ought to minimize false negatives, false assertions of no harm, and not false positives [75,178].

Objection (3) is correct insofar as specificity, as defined by Bradford Hill [75], requires a one-cause-one-effect relationship to support causal claims. However, epidemiologists admit that this definition of specificity is often not applicable because several different agents typically cause the same harmful effect, and vice-versa. Hence a better definition of causal specificity is that of Woodward: Some biological structures exercise fine-grained control over others, but not in the one-cause-one-effect sense. This notion of specificity is especially tied to the experimental-counterfactual requirement of showing that changes in purported causes are associated with changes in purported effects. For interventionists, causal associations are noncontingent largely because of their stability/invariance/specificity, qualities that are related to generalizations and lawlikeness [99].

Objection (4) likewise is correct in that typically in science, it is desirable to assess all competitor hypotheses, in order to assess some effect, such as neurodegeneration. However, accepting the neurodegeneration hypothesis is not superior to not accepting it, merely by virtue of having no competitor that provides an alternative causal explanation. It is superior because metals are well-known and well-accepted neurotoxins, many with no safe dose; because of the absence of strong evidence against the neurodegeneration hypothesis; and because of the presence of positive evidence for the hypothesis, evidence from three different causal-assessment methods (the mechanist, unificationist-coherence, and experimental-counterfactual). Using these three methods of causal assessment is reasonable, as already noted, because these methods are presumably what the US-EPA claimed to use to fail to accept the neurodegeneration hypothesis. Thus, if other scientists, including those of the US-EPA, rejected the neurodegeneration hypothesis, without proposing a competitor hypothesis, there is no great need to find such a competitor here.

4.3. Interpretation of the findings, their implications, and future directions for research

How is one to interpret preceding findings, supporting the neurodegeneration hypothesis? It appears that the generally low quality of studies—that scientists used as grounds for not accepting the neurodegeneration hypothesis—helps explain why the findings argue for accepting the hypothesis. These lower-quality studies fail in various ways, including ignoring dose and exposure data, failing to take account of confounders, not controlling study conditions, making false scientific assumptions about acute and chronic inflammation, demanding human-experimental studies of metals that are unethical-illegal, rejecting animal studies although they are dominant in toxicology, claiming different studies are "inconsistent" when they do not even make logical contact because they use different populations/methods/data/assumptions, and so on. All these errors suggest that studies that challenge the neurodevelopmental hypothesis must be interpreted with caution. Thus, the evidence used in this review is likely to be as good as it will get in the foreseeable future, mainly because so many different studies support the neurodegeneration hypothesis and reveal a unity across phenomena, subjects, and methods. Also, intuitively, it would be surprising if known neurotoxins could be conclusively shown to have no neurodegenerative effects, given the greater sensitivity of children

The preceding results are significant for both practical and theoretical reasons. On the practical side, they suggest that many victims of metals pollution—especially at smelters—are not being adequately protected by current metals standards. On the theoretical side, they suggest that much current science about smelters and metals' risks may be incomplete or flawed. As a result, both reasons suggest there may be sound scientific reasons for accepting the neurodegeneration hypothesis and, therefore, for strengthening environmental-metals standards.

Although these results are significant and important, much research remains to be done, especially to specify the sub-mechanisms—beneath the levels of the NOP mechanisms of neuroinflammation, oxidative stress, and protein build-up—that control neurodegenerative disease. In addition, given that some scientists believe there is an apparent lack of consensus about the neurodegeneration hypothesis, future research might also address any non-scientific reasons—such as financial conflicts of interest among metals' polluters—for some of this dissensus and the ways that experimental methods might to improved so as to achieve greater consensus.

5. Conclusion

Ultimately, the mechanistic, unificationist-coherence, and experimental-counterfactual methods of assessing causal claims accounts of causality suggest that—contrary to the US-EPA, smelter polluters, and some scientists—accepting the neurodegeneration hypothesis is more plausible than not accepting it. That is, this causal assessment suggests there is a causal link between heavy-metal/metalloid exposure and neurodegenerative diseases.

Conflict of Interest

All authors declare no conflicts of interest in this paper.

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