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Acute versus Chronic Exposures to Inhaled Particulate Matter and Neurocognitive Dysfunction: Pathways to Alzheimer's Disease or a Related Dementia

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Abstract

An estimated 92% of the world's population live in regions where people are regularly exposed to high levels of anthropogenic air pollution. Historically, research on the effects of air pollution have focused extensively on cardiovascular and pulmonary health. However, emerging evidence from animal and human studies has suggested that chronic exposures to air pollution detrimentally change the functioning of the central nervous system with the result being proteinopathy, neurocognitive impairment, and neurodegenerative disease. Case analyses of aging World Trade Center responders suggests that a single severe exposure may also induce a neuropathologic response. The goal of this report was to explore the neuroscientific support for the hypothesis that inhaled particulate matter might cause an Alzheimer's-like neurodegenerative disease, in order to consider proposed mechanisms and latency periods linking inhaled particulate matter and neurodegeneration, and to propose new directions in this line of research.

Keywords

Particulate Matter; Inhalations; Exposures; Neurodegeneration; Cognitive Impairment; Dementia; Neuroinflammation; Pathways; World Trade Center

Introduction

An estimated 92% of the world's population lives in areas with high levels of anthropogenic air pollution, which is responsible for an estimated 4.2 million deaths worldwide every year

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[1]. The plethora of evidence for the toxic effects of ambient air pollution, such as the combustion of fossil fuels, methane releasing waste landfills, fuming aerosols, and farmland fertilization, on the human body, the animal kingdom and the environment is alarming. Amidst its many deleterious effects, human and animal studies have recently identified that chronic exposures to air pollution impairs the central nervous system (CNS), which may result in neurocognitive impairments due to underlying neuropathology. In the present report, we synoptically review the literature for significant advances in our understanding of how such air pollutants can neurotoxically affect the CNS, both directly and indirectly. We also highlight results from our well-characterized cohort of World Trade Center (WTC) responders who were acutely exposed to inhaled particulate matter in both the dust plume and settled dust, as well as aerosolized particles that emerged from when the collapsed on September 11, 2001. We highlight the exposures WTC responders were subjected to as a case study for how severe acute and more chronic exposures to particulate matter may lead to neuropathology and resulting cognitive impairment, that could resemble hallmarks of Alzheimer's disease and related dementias (ADRD).

Air pollution refers to a complex mixture of excess solid, liquid and gaseous pollutants, of which the U.S. Environmental Protection Agency (EPA) has identified six 'criteria' chemicals: Carbon Monoxide, Lead, Nitrogen Oxides, Ozone, Sulfur Dioxide and Particulate Matter (PM), the latter of which is borne from four aerodynamic diameters: *coarse* (PM₁₀; <10µm), *fine* (PM_{2.5}; <2.5µm), *ultra-fine* (UFPM<0.1µm) and *nanoparticles* (nPM<50nm). Other air pollutants include, but are not limited to Acrolein, Asbestos, Benzene, Carbon Disulfide, Creosote, Fuels Oils/Kerosene, Polycyclic Aromatic Hydrocarbons (PAHs), Synthetic Vitreous Fibers, Total Petroleum Hydrocarbons (TPHs). These airborne pollutants can affect anyone. While researchers in government agencies, health organizations, and private industry strive to find ways to reduce anthropogenic pollution in accordance with to EPA and other global regulatory standards, these chemicals are likely to linger in our atmosphere for extended and chronic periods of time, rendering their study both timely and of paramount importance for understanding the impact on human and animal health.

Historically, research on the effects of air pollution has focused on cardiovascular and pulmonary health [2–4], but emerging evidence is systematically demonstrating that chronic and acute exposures to PM are associated with neurodevelopmental disorders [5] and neurodegenerative diseases such as ADRD [5–8]. Moreover, the underlying etiological mechanisms for these observations is not only the result of direct inhalations of PM_{2.5} and UFPM in the brain via pulmonary and olfactory entrance, but also indirectly to the brain from their uptake in peripheral systems, which can induce neuroinflammatory and oxidative stressors that are subsequently neurotoxic to the CNS, resulting in neurocognitive decline [9]. Cognitive impairment presents a high-risk prodrome to dementia [10–12], of which ADRD is the most common cause and, in addition, acts as a major contributor to old-age mortality [13]. ADRD has a long prodromal phase with molecular, structural, and functional changes commencing decades prior to the onset of observable symptoms. According to the recent NIA-AA framework [10–12], ADRD is characterized by progressive accumulation of an underlying neuropathological cascade commencing with (A) β-amyloid deposition,

thereby forming neuritic plaques [14], followed by (T) neurofibrillary tau tangles [15] and (N) grey matter atrophy/neurodegeneration [10].

While there is an increasing view that cognitive performance may decline as a result of chronic exposures to PM, it is not clear whether severe and acute exposures to inhaled PM in early life might result in a similar process of neurodegeneration and, if so, what the process might be. In this review, we first detail the relevant WTC exposures and provide a timeline for their occurrence. We then go on to synoptically examine how an acute, but severe, inhaled exposure to airborne pollutants, including particulate pollutants, might cause deleterious effects on the CNS, leading to cognitive impairment (CI) and whenever possible, outline how they interface with the pathogenesis of ADRD. Our present examination of the extraordinary WTC dust exposures that responders were subjected to, provides a unique perspective for the acute and chronic effects of inhaling PM on the nervous system, insofar as that they can demonstrate a temporally condensed case study and elucidate how these findings link with the current state of the literature.

WTC Dust Cloud Exposures

Toxic exposure to PM may be experienced while inhaling air of reduced quality while undertaking routine activities during normal life but may also be experienced as a pulmonary shock that overwhelms the system. This overwhelming toxic exposure provides a critical lens with which to understand the impact of acutely inhaled PM in CNS dysfunction and specifically ADRD pathogenesis, since such exposures can induce neuroinflammatory and neurodegenerative responses such as those reviewed above.

On 9/11/2001, an unprecedented number of residents of, and workers in New York City were acutely dosed with a severe pulmonary exposure to dust from the collapsed World Trade Center, located on Manhattan's lower West Side. Individuals caught in the dust cloud were exposed to a vast array of inhaled exposures, lodging PMs in both their lungs and gut. There has been substantial documentation of PM exposures arising from the dust cloud originating from the initial collapse of the towers, and subsequently, on the settled dust – predominantly, the re-aerosolized PM in the weeks and months that followed. However, as we will emphasize, this second and more enduring exposure may have been a more potent and detrimental neurological exposure, as the longer-term inhalation of specific subtypes of PM are more likely to cause systemic changes consistent with neurodegenerative disease. However, this is more challenging to measure since it is both temporally distant from the WTC events and is also less likely to be identified and reported by unbeknownst responders, as the inhaled dust is miniscule.

Reviewing WTC air quality studies does, however, help us to better understand the nature of these exposures. For example, in the days and weeks following 9/11/2001, Liou et al., collected and analyzed dust from sites along three streets near the WTC and while suggesting that more than 95% of the dust were $>PM_{10}$, they also reported that ~1.5% of the dust was made up of PM_{10} and that significant amounts of PAHs were detected from dust measured across all three measurement sites [16]. Further detectable elements in dust at all three sites identified nearest the WTC included strontium, barium, lead, aluminum, thallium,

and manganese, among others. Interrogating this further, Landrigan, Lioy, et al. then noted that airborne exposures to PM_{2.5} were elevated in sites surrounding the WTC for more than six weeks following the WTC disaster, while also noting that PAH exposures near the WTC site was heaviest in the week after the 9/11/2001 event and remained as much as ~12 times higher in the following month [17]. However, high PM₁₀, PM_{2.5} and PAH exposures lasted well into January 2002 as the only remaining inhaled exposures, as many of the coarser materials had settled and may have been removed (as shown in Figure 1) [18, 19].

To better understand the detrimental neurocognitive effects of WTC dust cloud exposures present in responders presently at midlife, we must first explore the current state of the literature with regards to PM exposures and neurobiological effects.

Fine Particulate Matter (PM_{2.5})

Analyses of global variations in the chemical composition of PM_{2.5} revealed that the majority of anthropogenic contributions include approximately 20% ammoniated sulfate, ~13% crustal material, ~12% black carbon, ~5% ammonium nitrate, ~1% trace element oxides and ~40% residual matter [20]. According to the EPA, these atmospheric aerosols are mostly formed as secondary particles in the atmosphere as a result of the combustion of fossil fuels from power plants, industrial facilities, mobile and other sources of combustion [21].

The detrimental cognitive effects of chronic PM_{2.5} exposures received early and detailed attention from a provincial group of scientists in Mexico City, who demonstrated associations with a diversity of neuropathologies such as white matter glial apoptosis, disruptions in the Blood Brain Barrier (BBB), oxidative stress, neurovascularization and neuroinflammation, along with evidence of A, T and N in canines, children and young adults [22–29]. Furthermore, a large prospective community study of non-demented older women (aged 71–89 years old), demonstrated that higher PM_{2.5} exposures displayed significant reductions in white matter, with effects reported in the frontal and temporal cortex and the corpus callosum, which the authors stated was equivalent to 1 to 2 years of brain aging [30]. A German cross-sectional study of 50–80 year-olds demonstrated that PM_{2.5} exposures are positively associated with higher aMCI [31]. This likely reflects prodromal AD with structural MRI changes showing associations with volumetric decreases in the hippocampus, entorhinal cortex, amygdala, fusiform gyrus, precuneus and the isthmus of the cingulate gyrus [32]. Moreover, a large U.S. study of older adults (55+ years old) exposed to high levels of PM_{2.5} demonstrated a 1.5 times higher error rate in cognitive domains of working memory and orientation [33] and another large population study (mean age 60.5 years old) in Los Angeles revealed that increasing PM_{2.5} exposures were associated with lower verbal learning [34]. Similarly, a large study of Great London residents (mean age 66) displayed that higher PM_{2.5} exposures associated with longitudinal decline in standardized memory scores [35] and a prospective study of community dwelling seniors in Boston demonstrated that residential proximity to major roadways was associated with poorer performance on cognitive tests of verbal learning and memory, psychomotor speed, language and executive functioning [36] - though important to note is that this latter study did not distinguish PM subtype exposures. Additionally, a prospective cohort study of primary school children

(mean age 8.5) from 39 schools in Barcelona revealed that traffic-related PM_{2.5} was associated with reductions in cognitive growth equivalent to 22% of the annual change in working memory, 30% of the annual change in superior working memory, and 11% of the annual change in the inattentiveness scale. It concluded that traffic was the only source of fine particles associated with a reduction in cognitive development [37].

PM_{2.5} can more readily enter the brain by penetrating through the olfactory epithelium and can then travel deep into the airways and lungs, infiltrating blood circulation and ultimately crossing the BBB, which can induce oxidative stress and neurotoxicity through transient receptor potential melastatin 2 (TRPM2) channel pathways [38, 39]. To better understand underlying molecular mechanisms for these phenomena, animal studies working with one-month old male mice exposed to concentrated PM_{2.5} for six hours. The mice demonstrated a higher latency in locating the escape hole and a higher number of location errors in a Barnes maze task, along with depressive-like responses and impairments in spatial learning and memory, which were attributed to decreased apical dendritic spine density and dendritic branching in the hippocampal CA1 and CA3 regions, respectively [40]. Developmental studies with Wistar male rats exposed to PM_{2.5} who were assessed for short term memory performance using spontaneous nonmatching to sample recognition tests analogous to novel object recognition, demonstrated significant reductions in discrimination and less exploration time of novel objects after 150 days of exposure. The authors identified a potential underlying mechanism being cortical oxidative stressors, as they reported increases in Malondialdehyde (MDA) [41]. Using adult Sprague-Dawley male rats (2 months old), it was demonstrated that intra-tracheal injection of PM_{2.5} for up to a year damaged sensory functions as well as learning and memory as a function of ultrastructural changes in mitochondria and neuronal myelin sheaths, along with abnormal expression of apoptosis-related proteins (Caspase-3, Caspase-9) [42]. Studies with male C57BL/6 mice subjected to concentrated PM_{2.5} inhalations demonstrated that after nine months of exposure, there was a significant increase in beta-site amyloid precursor protein (APP) cleaving enzyme (BACE) protein levels, APP processing, and A β ₄₀ levels, lending credence to the A component of the ATN model for AD. Furthermore, these molecular changes correlated with a concomitant increase in Cyclooxygenase-1 (COX-1) and COX-2 protein levels, changes in the cytokine profile and synaptic alterations as a function of increased postsynaptic density protein 95 (PSD95) expressions sans presynaptic protein synaptophysin. The authors argue that prolonged exposures to PM_{2.5} has the potential to alter mechanisms of neuroinflammations and promote development of early AD-like pathology [43].

Further molecular mechanistic insights come from studies with human neuroblastoma SH-SY5Y cells [44]. It was demonstrated that 24-hour exposures to PM_{2.5} led to changes in mitochondrial dynamics such as swelling, the opening of mitochondrial permeability transition pore (mPTP) and decreases in Adenosine Triphosphate (ATP) levels, mitochondrial membrane potentials, DNA copy numbers, fission/fusion genes (Drp1 and OPA1), which affected the gene expression of CypD, SIRT3 and COX IV. Furthermore, the authors reported increases in cellular reactive oxygen species (ROS), Ca²⁺ and A β ₄₂ levels and inhibition of manganese-superoxide dismutase (SOD2) activities, reduction of GSH levels GSH/GSSG ratio and elevation of mitochondrial MDA contents. The authors argue that such mitochondrial dysfunctions and generation of oxidative stressors are some of the

major underlying molecular mechanisms for PM_{2.5} induced neurotoxicity [45]. Taken together, there is a plethora of evidence that link PM_{2.5} exposures to neurocognitive decline, neuroinflammation, neurotoxicity and ADRD-like neuropathology.

Ultra-Fine Particulate Matter (UFPM)

Diesel emissions are a major component of UFPM exposures and are the product of internal combustion exhausts and are a known carcinogen [46, 47], with chemical contents belonging mostly to the size category of UFPM [48]. Diesel inhalations have been demonstrated to cause elevations in interleukin-6 (IL-6), nitrated proteins, and ionized calcium-binding adaptor molecule 1 (IBA-1) – a microglial marker. These changes promote neuroinflammation and increases in tumor necrosis factor- α (TNF α), IL-1 β , IL-6, macrophage inflammatory protein-1 α (MIP-1 α) receptor for advanced glycation end products (RAGE), fractalkine, and the IBA-1 microglial marker in multiple brain regions, along with increased microglial IBA-1 staining in the substantia nigra, and finally, global elevations in TNF α [49]. These observations highlight complex, interacting mechanisms for how diesel exposures, and to a wider extent UFPM exposures, may cause neuroinflammation and neurotoxicity. Similarly, acute diesel exposures in C57BL/6 mice significantly increased lipid peroxidation of pro-inflammatory cytokines (IL-1 α , IL-1 β , IL-3, IL-6, TNF- α) in various brain regions, in particular, the olfactory bulb and hippocampus. In addition, the authors reported these changes in collocated regions such as the entorhinal cortex, along with activated microglia as a function of increased expressions in ionized calcium-binding adapter molecule 1 (Iba1) and translocator protein TSPO binding. This lends further evidence in support of the hypothesis that diesel exposures are neuroinflammatory, generate oxidative stress and ultimately lead to neurotoxicity in the brain [50].

nano-Particulate Matter (nPM)

nPM includes the smallest of particles, sizing in at 1–200nm, which requires the use of electron microscopy to visualize them, as they are too small for ordinary optical microscopes. Being so small, nPM can most readily enter the body through pulmonary systems, translocating beyond the lungs to the both the cardiovascular and central nervous systems, simultaneously entering blood circulation, leading to inflammation and oxidative stress to other organs [51]. Inhaled nPM can enter the CNS through olfactory pathways, highlighting a severe exposure route to neurotoxic effects [52]. To further highlight this exposure route, animal studies with adult mice exposed to re-aerosolized nPM for 5, 20, and 45 cumulative hours over 3 weeks, demonstrated rapid increases of 4-hydroxy-2-nonenal (4-HNE) and 3-nitrotyrosine (3-NT) protein in the olfactory neuroepithelium (OE) and the olfactory bulb (OB), with all brain regions demonstrating increased levels of TNF α protein by 45 hours. In addition, the mice demonstrated earlier induction of TNF α mRNA in OE and OB, corresponding with mixed glial responses in in-vitro OE, with rapid induction of nitrite and inducible nitric oxide synthase (iNOS), followed by induction of TNF α , signifying oxidative stress and inflammatory responses to nPM between the OE and the brain [53].

Animal studies examining neuritic atrophy, white matter degeneration, and microglial activation in the hippocampus of young and middle-aged C57BL/6J mice exposed to nPM, demonstrated that young mice showed selective changes in the CA1 region such neurite atrophy, decreased white matter myelin basic proteins (MBP) and Glutamate receptor 1 (GluR1) proteins, and increased Ionized calcium binding adaptor molecule 1 (Iba1) and TNF α mRNA. However, the authors reported diminished effects of nPM exposures in older mice, suggesting an age ceiling effect, and further argued that the selective vulnerability of the CA1 of young mice parallels the observed CA1 vulnerability in AD [54]. Likewise, recent work further interrogating this model has noted that exposures to nPM additionally excited an amyloidogenic response by increasing oxidative damage to the lipid rafts and altering APP processing, with one interpretation of these results being that such exposures might cause an Alzheimer's-like dysfunction, resulting, in part, from over-production of AB that may be unique to exposure-related diseases [55]. Furthermore, examinations of female EFAD transgenic mice (5xFAD+/-/human APOE- ϵ 3 or ϵ 4+/+) with 225 hours of nPM exposure over a period of 15 weeks demonstrated increased cerebral A β deposits, A β oligomers, selective atrophy of hippocampal CA1 neurites and decreased GluR1, whereas female wildtype counterparts also showed nPM-induced CA1 atrophy and GluR1 decrease, with in-vitro nPM exposures in neuroblastoma cells (N2a-APP/swe) demonstrating increased pro-amyloidogenic processing of APP. This suggests that nPM exposures promote pathological brain aging with potentially a greater impact in APOE- ϵ 4 [56]. These findings lend support to the notion that nPM exposures contribute to the A component of the ATN model for ADRD.

Neuroinflammatory studies demonstrated that nPM exposure elevated in IL-1 β , IL-3 IL-6, TNF- α and MDA in the hippocampus, and that such brain inflammation and oxidative stress were noticeably higher in male mice than in female mice, suggesting sex differences [50]. A study examining glial TNF α production in mixed glia (astrocytes and microglia) derived from neonatal rat cerebral cortex, demonstrated that microglia contributed more to TNF α induction than astrocytes when exposed to nPM [57]. Furthermore, nPM exposures in C57BL/6J male mice demonstrated reactive microglia and a two-fold increase in the local deposition of complement C5/ C5 α proteins and complement component C5a receptor 1 (CD88) in the corpus callosum, which indicate that the interaction between such anaphylatoxins and activated microglia may play an important role in white matter injury following nPM exposure [58]. A study evaluating three month old C57BL/6J male responses to chronic inhalations of reaerosolized nPM displayed altered neuronal and glial activities, insofar that GluA1 was decreased in the hippocampus, whereas glia were activated with the subsequent inductions of (IL-1 α) and tumor necrosis factor- α (TNF α) inflammatory cytokines in cerebral cortex, with in-vitro hippocampal slice cultures showing that 24–48 hour nPM exposures increased the neurotoxicity of N-methyl-d-aspartic acid (NMDA) along with impaired neurite outgrowth in embryonic neuron cultures. The authors argued that nPM can affect embryonic and adult neurons through glutamatergic mechanisms, but also that cerebral ischemia, which involves glutamatergic excitotoxicity, could be exacerbated by nPM [59]. Moreover, investigations of high dose nPM-rich diesel exhaust exposures in hippocampal-dependent spatial learning and memory function-related gene expressions in BALB/c female mice for three months, displayed higher mRNA expression levels of the

NMDA receptor subunit NR2A, the proinflammatory cytokine CCL3, and brain-derived neurotrophic factor (BDNF), along with a longer time to reach the hidden platform in the Morris water maze [60]. In a follow up study, the authors demonstrated that the same high exposures to nPM diesel exposures disabled the mice from discriminating between familiar and novel object recognition, a decrease in the expression of glutamate transporter EAAT4 and an increase in glutamic acid decarboxylase GAD65, along with prominent activation of microglia in the hippocampus, suggesting that genes related to glutamate metabolism may be involved in the nPM rich diesel exhaust exposure-induced neurotoxicity [61]. Likewise, in a study using filter-eluted nPM sans PAHs, it was reported that in vivo exposure of adult male mice to re-aerosolized nPM for 3 weeks resulted in the induction of IFN γ and NF- κ B and that gestational exposure to nPM caused equivalent depressive behaviors in the forced swim cognitive test, but the effect was greater on males than females [62]. Taken together, using both in vitro cells cultures and *in vivo* rodents, there is evidence to suggest that nPM exposures initiate neuroinflammation and subsequent neurotoxicity *via* proinflammatory cytokines from microglia that contribute to neurocognitive decline and that may lead to the genesis of ADRD [63, 64].

Nitrogen Dioxide (NO₂)

NO₂ is a gaseous product of fossil fuel combustion, and the main source of nitrate aerosols, which form an important fraction of PM_{2.5} [1]. Examining a cohort of elderly women (mean age 74.1 years) living next to a busy road with more than 10,000 cars per day in Germany for over 20 years, Ranft, et al., reported that background concentrations of PM₁₀ and traffic-related PM were consistently associated with lower cognitive performance in a dose-dependent manner [32, 65]. Specifically, for PM₁₀ these studies reported that neurocognitive effects to NO₂ exposures were strongly dependent on residential distance to the road, and displayed a distance-dependent drop in neuropsychological test scores. In two large cohort studies in the northern Manhattan area of New York City, an increase in NO₂ exposures resulted in lower global cognitive scores at enrollment and more rapid decline in cognitive scores between visits, and together with similar observations from PM_{2.5} and PM₁₀ exposures, the authors argued that exposures to air pollution has adverse effects on cognitive aging and brain health [66]. Furthermore, NO₂ exposures are associated with olfactory dysfunction [67], increase in ischemic stroke [68, 69], reduced psychomotor development during childhood [70], depression [71], memory decline [34, 72], cognitive decline [73, 74], amnesic mild cognitive impairment (aMCI) [31], cortical thickness in AD signature regions (entorhinal, inferior and middle temporal, fusiform, posterior cingulate, precuneus and supramarginal gyri) [75] and incidence of dementia [76, 77]. Additionally, animal studies have demonstrated that direct NO₂ inhalation caused a worsening of spatial learning and memory and promoted dose-dependent A β deposition [78], while other studies have reported that direct NO₂ inhalations promote proinflammatory mechanisms that originate from the periphery, which then translocate to the brain [79–81], excitotoxically disrupting synaptic plasticity mechanisms of learning and memory such as long-term potentiation (LTP) [82]. Finally, NO₂ inhalations were shown to induce tauopathy by disturbing the insulin signaling pathway via p38 MAPK and/or JNK activation and IRS-1/AKT/GSK-3 β attenuation [83]. Taken together, there is strong evidence that *chronic exposure* to high levels

of anthropogenically released NO₂ in the atmosphere can lead to the genesis of neurocognitive symptoms as a function of ATN that may lead to ADRD.

Polycyclic Aromatic Hydrocarbons (PAHs)

PAHs are produced from the incomplete combustion of organic materials such as coal, oil, gas, wood, garbage, tobacco and as part of diesel exhaust particulates, which then accumulate in our breathable atmosphere. In a sample of elderly Americans over 60 years of age, PAHs were shown to be negatively associated with working memory [84]. Elderly adults notwithstanding, PAHs have been further demonstrated to be harmful to the developing fetal brain, longitudinally extending into childhood as revealed by a depressed verbal IQ measure [85]. Moreover, prenatal exposures to PAHs contributed to slower processing speed, attention-deficit/hyperactivity disorder symptoms, and externalizing problems in urban youth by dose-dependently disrupting the development of left hemispheric white matter, whereas postnatal exposures to PAHs contributed to additional disturbances in the development of white matter in bilateral dorsal prefrontal regions [86]. Furthermore, studies investigating exposure to PAHs in New York city five-year-old children demonstrated an adverse drop in cognitive performance [87] and suggested that they may play a role in childhood Attention Deficit Hyperactivity Disorder (ADHD) behavior problems [88].

While the underlying mechanisms by which PAHs may render such neurocognitive impairments are not fully understood, human and animal studies have implicated endocrine dysfunction [89–91], disruption of placental growth factors that lower oxygenation and nutrition during fetal development [92], DNA damage of the embryoprotective p53 pathway causing missed checkpoints in the cell cycle that trigger neuronal apoptosis [93–95], neurotoxicity via oxidative stress [96] and inhibition of homeostatic DNA methylation [97]. Since PAHs are hydrophobic and can remain in the body for weeks, they can accumulate to a critical dose in the periphery, which can permeate the lipophilic blood-brain-barrier membrane contributing to a plethora of pathologies, including the induction of neurological diseases [98]. Finally, PAHs have been shown to modulate A β aggregation through the possible formation of micelle-like A β -PAH co-aggregates that may induce fibril-forming aggregation pathways [99]. Taken together, while more studies are required to uncover the underlying mechanisms of how PAHs affect the CNS, there is evidence nevertheless that they partake in the AN component of the ATN model for ADRD.

Neurocognitive Effects of WTC Dust Cloud Exposures

We have seen how exposures to PM_{2.5} can more readily enter the brain and cause oxidative stress, neurovascularization, neuroinflammation, reductions in white matter density and accelerated brain aging along with evidence of A, T and N. Likewise, PM_{2.5} exposures have been linked with higher aMCI and volumetric decreases in the hippocampus, entorhinal cortex, amygdala, fusiform gyrus, precuneus and the isthmus of the cingulate gyrus, which are all signature ADRD regions, in addition to overall decreases across cognitive domains. Furthermore, since PAHs are hydrophobic and can remain in the body for weeks, they can have detrimental effects on white matter density, working memory, cognitive performance,

exacerbate neuroinflammation and modulate A β aggregation, all of which contribute to significant neurodegeneration. Taken together, WTC exposures to PM₁₀, PM_{2.5} and PAH may have indeed had a pronounced neurodegenerative effect on responders, affecting their neurocognitive performance as time has passed. Knowledge of these effects offers an investigative platform for which to monitor specific WTC exposures in the cognitive and neurobiological domains of responders. Indeed, as we will outline below, previous and ongoing investigations of exposed WTC responders are suggestive of the above phenomena, but also highlight the need for further study to clarify the types of exposures, specifically within the context of delineating the duration of PM_{2.5} exposures in each responder, and their subsequent observable symptoms and pathology.

Recognizing that WTC dust exposures may also have independent effects on CNS functioning, Clouston *et al.*, employed highly sensitive computer-administered measures of memory and processing speed in WTC responders and discovered that long-term exposures to the WTC geographic domain resulted in a systematic reduction in functioning across all tested domains of cognition [100]. Further research has also reported that such exposures are associated with increased incidence of MCI, with APOE4 carriers identified as being at higher risk [101]. Likewise, recent neuroimaging work in our lab has demonstrated that cortical atrophy in WTC responders with MCI is present throughout the temporal lobe [102, 103], in a pattern that is consistent with recent work in individuals chronically exposed to high levels of air pollution [104].

Taken together, these results suggest that the impact of not only acute and severe, but chronic mild exposures to PM₁₀, PM_{2.5} and PAHs, during the search and rescue efforts following the WTC disaster, might have incited accelerated brain aging and, perhaps, even caused an emerging neurodegenerative disease, almost two decades later. However, the above reports of WTC and general population exposures to PM and detrimental CNS effects raise an important discussion regarding our understanding for the temporal latency period from time of PM exposure to the presentation of observable symptoms.

Latency periods between PM exposures and the presentation of symptoms

In the research community, we have seen, a growing body of evidence that supports the hypothesis that inhaled PM is likely to cause AD/DRD. The causal chain in these studies consistently identifies linkages between inhaled PM to neuroinflammation and neurodegeneration. Collating and visualizing this information together into pathways, reveals that PM exposures are often articulated as linking inhaled PM either through a process of neural infiltration, which results in neurotoxicity (solid pathway in Figure 2), or through a process of chronic inflammation (dashed pathway in Figure 2) or, more likely, through a mixed process (incorporating dotted lines with solid and dashed lines in Figure 2).

Illustrating these pathways can be informative, as it could better elucidate how the response to inhaled PM can cause an aging-related disease with a potentially very long latency period. However, integrating a consideration for the effect of an acute and severe exposure among fully-grown adults, such as that from when the WTC towers collapsed, challenges researchers to explicitly consider the mechanisms linking such a one-time exposure to

outcomes decades later. Moreover, individuals chronically exposed to lower levels of PM poses an equally challenging study. These considerations indicate the requirement to identify and integrate a latency period in PM exposure-induced AD pathogenesis as it is becoming increasingly clear that such acute and pronounced, or chronic and low-level exposures to airborne pollutants may result in different pathways to disease with different underlying mechanisms, characteristics, and by necessity, different risk factors.

The least restrictive view for a pathway lies within inhaled PM causing a chronic inflammatory response to chronic PM exposure thereby eliciting a concomitant chronic neuroinflammatory response (Figure 3). While this theory does provide a mechanism for both old age vulnerability to neurodegenerative diseases, since it suggests that age-related increases in risk likely result from the timing needed to cause immune-regulated damages, it is not clear whether such a neuroinflammatory cascade is feasible when considering a single inhaled exposure occurring in early adulthood or at midlife. Rather, it appears to suggest that chronic, perhaps lifelong exposures, are necessary to sustain a sufficient immune reaction necessary to render neural damage. Nevertheless, this pathway circumvents the need for PM exposures to cross the BBB, since these processes engage a neuroimmune cascade that might allow a pathway for which materials that are too large or irregular in shape and unable to cross the air-blood barrier (ABB) or BBB, to persist a more chronic deleterious neurological effect with latency periods that are chronically being refreshed.

Studies in Germany, New York City and other areas of high pollution reported that residing with chronic exposure to non-neurally infiltrating PM such as NO₂, resulted in globally lower cognitive performance as a function of accelerated brain aging with the emergence of aMCI and reduced cortical thickness in AD signature regions. Moreover, animal studies reveal that such exposures promote the translocation of peripheral inflammatory responses to neuroinflammatory cascades that lead to evidence for changes in the ATN model. Furthermore, chronic PAHs have been reported to be detrimental to the developing and developed brain with white matter volume disturbances, endocrine dysfunctions and since they can remain in the body for weeks, can inflect chronic neuroinflammation with evidence of developing the AN component of the ATN model for ADRD. Therefore, this pathway illustrates how chronic PM exposures that do not neurally infiltrate can lead to systematic immunologic responses in the periphery can lead to neurodegeneration.

An alternative pathway to the one above, hypothesizes that inhaled PM enters solely through the periphery, thereby causing pathology in the body via chronic reactions to foreign pathogens that cannot be cleared from the periphery (Figure 4). In effect, this pathway suggests that low-grade inflammation indicates not necessarily a cascade, but rather a sustained immunologic response to the presence of a material that *need not actually be directly neurotoxic*, but rather must be located in a place where the body cannot naturally rid itself of these particles, or else be of particular nature such that it cannot be readily captured and removed from the body. In such as case, a single exposure with a toxic material would sufficiently have the potential to cause a chronic immune response, in part because these lodged PM in the periphery might inhabit the lungs or gut, and may additionally infiltrate the blood, but would not necessarily infiltrate the brain but nevertheless elicit an auxiliary and chronic neuroinflammatory response that leads to neurodegeneration. In this pathway,

the latency period may indicate the influence of systemic and systematic immune responses elevating the risk of a neuropathological cascade, either because the neuroimmune response may cause the cascade or because the elevated glial activation may accelerate the proliferation of ATN changes generated via an independent process.

Likewise, an alternative pathway may present to the brain more directly, but also more stochastically by relying on the systemic vulnerabilities to infiltration of neurotoxic materials directly into the brain as the main neuroinflammatory and neurodegenerative mechanism. Specifically, PM inhalation might either enter the brain in one of at least two ways; indirectly via proliferation from the ABB into the blood as seen in Figure 4, but with an additional caveat that it *must additionally cross the BBB*; or, infiltrate the brain directly *via* transduction from the olfactory cortex. In either case, for such a pathway to be engaged, the presence of neurotoxic PM must be either immediately or eventually physically present within the brain itself. Neuroinflammation, would then emerge as a direct response to PM and may cause neurodegeneration to emerge in specific, affected regions of the brain. For example, where PM first infiltrates the brain, it may subsequently proliferate slowly to other regions passively distributed via cerebrospinal fluid dynamics or actively distributed by glia, which would ineffectively phagocytose PM and end up distributing it throughout the brain when they regurgitate indigestible infiltrate. This theory helps to explain potentially long latency periods and because PM must infiltrate the brain.

Indeed, there is a plethora of evidence to suggest the existence of such a directly neurotoxic pathway, with early evidence stemming from research in Mexico City which demonstrated that PM_{2.5} infiltrate disrupted the BBB, and caused oxidative stress, neurovascularization and neuroinflammation along with evidence of A, T and N in canines, children and young adults. While other studies with direct PM_{2.5} exposures displayed white matter disruptions, accelerated brain aging, higher incidence of aMCI, working memory, orientation, and verbal learning deficits along with other cognitive impairments. Mechanisms of neurotoxicity have been implicated TRPM2, COX and PSD95 channel pathways, hippocampal neuron spine density reductions and oxidative stress along with mitochondrial and myelin sheath disruptions and changed in the A component of the ATN model for AD. Likewise, evidence for this model can also be derived from UFPM exposures, where direct inhalations promote complex neuroinflammation and neurotoxicity, at the olfactory, hippocampal, and entorhinal regions. Moreover, nPM, the smallest of particle pollutants, lend further credence to this model as their neural infiltration, whether directly from the olfactory cortex or crossing the BBB from peripheral circulation, do also lead to complex neuroinflammation, neurotoxicity and resulting neurodegeneration, also with changes in the A component of the ATN model for AD.

Taken together, the above hypotheses modelling particulate matter exposures and their effects on the CNS are not only useful in furthering our understanding for potential mechanisms of cause and effect, but also provide a foundational understanding that pragmatically, it may often be the case that a combination of these models is in effect. Potential strategies aiming to distinguish between these three temporal models must first employ identification of PM aerosol sizes in the exposures. For example, if it is known that inhaled PM exposures involved PM small enough to cross the BBB for direct neural

infiltration, then such an observation would lend more credence to considering the model displayed in figure 5. If such PM exposures are known to be chronic, then the model portrayed in figure 3 may be more likely, with or without the concurrent presence of the model in figure 5. Knowing the specific size, amount and chronicity of PM exposures would better serve to answer the latter question, insofar in that if there is a large, transient exposure to finer PM size, the neural infiltrate model is highly likely to be in effect, whereas chronic, low-level exposures to finer PM sizes would likely engage the immunologic response model, with some consideration of the neural infiltrate also. However, if individuals are exposed to larger PM sizes that cannot cross the BBB, then it is more likely that detrimental neurocognitive effects would arise indirectly through the systemic entry model in figure 4, and if chronic, would also contain elements from the immunologic response model. Therefore, in order to effectively consider and apply one of the above proposed models for temporal latency between PM exposures and observable neurocognitive symptoms, appropriate classification of PM sizes in exposures are paramount before proceeding.

Potential Synergistic Effects with pre-existing risk factors

Many of the above theories rest on the ability for NPM to infiltrate the brain. A number of known conditions are believed to influence BBB permeability and may therefore augment any effects of additional exposures or of infiltration into the brain when potentially toxic material remains chronically distributed throughout the exposed person's system following a severe exposure. One crucial component of these exposures at midlife include exposure-related psychiatric conditions such as posttraumatic stress disorder (PTSD) or major depressive disorder (MDD). Evidence from animal models has demonstrated that such traumatic events can trigger neuroinflammation and neurodegeneration [105], and that bouts of stress can disrupt the BBB [106], are associated with an increased risk of cardiovascular disease [107, 108], and increased distribution of c-reactive protein [109], potentially accelerating PM infiltration and its detrimental effects on the brain. However, recent studies in animal models are highlighting molecular mechanisms of resilience to BBB disruptions in neurobehavioral mood disorders [110]. Furthermore, PTSD is often co-existent with traumatic brain injury [TBI] [111], for which there is a plethora of evidence for BBB disruptions in TBI [112–114], which can further augment the detrimental effects of any concurrent PM exposures on the brain. Vascular compromise of the BBB can also be detected in individuals carrying the apolipoprotein E4 (APOE4) AD susceptibility gene [115, 116], individuals with hypertension [117] and those who have suffered from ischemic stroke [118, 119], which once again, can potentially further exacerbate PM induced neurodegeneration. Therefore, future research strategies that can effectively measure such pre-existing risk factors can help disentangle and elucidate an individuals' detrimental susceptibility to PM exposures, aiding in the identification and classification of high risk and/ or resilient groups.

Measuring the size and source of PM exposures would serve as one, albeit major avenue in delineating which temporal pathway is involved between the latency period of exposure and observable neurocognitive symptoms, however, establishing which model has taken effect may require post-hoc analysis from when observable symptoms and/or pathology has arisen. For example, imaging studies employing PET radioligand biomarkers may be able to

identify relevant neuropathology as a result of known prior PM exposures. Alternatively, post-mortem histopathology for such biomarkers may serve as a standard of truth for the presence of neuropathology for which to associate known exposures with. Nevertheless, since PM exposures can be small and invisible, and can persist chronically or incur acutely with a large dose, such as that seen when the WTC towers fell, it is recommended for the research community to have appropriate measures in place in order to, at-the-very-least be able to appropriately characterize the size and nature of the offending PM exposures.

Potential Strategies to Differentiate between the temporal models

The three hypotheses noted above differ in a number of critical ways. First, more research is needed that examines the role of pre and post-WTC exposure activities that may be augmenting any potential inflammation, so as to determine to what extent the WTC exposures were capable of acting alone or if instead they catalyzed existing or follow-up exposures as suggested in Figure 3. Second, we have determined that WTC PTSD is associated with immunologic dysregulation evident in peripheral markers [120–123], however no work to date has examined whether WTC exposures directly resulted in immunologic dysregulation. Further work is, therefore, necessary to detect whether the presence of a neuroinflammatory environment is feasible as suggested in Figure 4. Finally, there is a difference in mechanism that can be reliably examined only using novel methods to either detect the presence of chronic non-biologic WTC particulate matter in the brains of WTC responders. This last effort requires that individuals provide neuronal tissue at time of death for post-mortem histopathological analyses and would be central to determine whether WTC dust might have infiltrated the brain as hypothesized in Figure 5.

Conclusions

Inhaled PM is ubiquitous and invisible, making it especially difficult to identify relationships between exposures and symptoms. However, it is also unique in having the chemical structure necessary to act as a neurotoxin and is also able to concurrently incite an immune response, while also, under the right circumstances, filter through the blood-brain barrier. In the present report, we highlighted an increasing number of studies that have identified several pathways linking inhaled neurotoxic materials to incidence of ADRD in old age, along with evidence for the ATN model of ADRD. We then drew examples from our own work with the WTC population exposures from when the towers collapsed on 9/11, along with providing theoretical frameworks highlighting the importance of latency periods between PM exposures and subsequent detrimental CNS effects. Further work is required to determine the degree to which PM exposures are attributable for sporadic ADRD. However, it is also critical that we improve detection methods to better distinguish mechanisms linking inhaled PM subtypes with ADRD as such factors may concurrently provide novel treatment targets necessary for policymakers to protect future generations from chronically debilitating neurological diseases. Such efforts will greatly benefit the furthering of our understanding of how PM exposures affect the CNS, not only in the WTC exposed responders, but also the increasingly at-risk world population.

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Figure 1.
Temporal changes in exposure intensity to neurotoxic materials in the weeks to months following the attacks of 9/11/2001

Figure 2.
Previously hypothesized pathways linking inhaled PM and neurodegeneration.

Figure 3.
Pathway for temporal dynamics linking chronically inhaled PM with neurodegenerative disease via an *Immunologic Response*

Figure 4.
Temporal dynamic pathways wherein inhaled PM accelerates an ongoing neuropathological process via *Systemic Entry*

Figure 5. Temporal dynamic pathways linking inhaled PM infiltrating directly into the brain and causing a latent neuropathological process via *Neural Infiltration*