Published in final edited form as:
Neurotoxicology. 2012 October ; 33(5): 972–984. doi:10.1016/j.neuro.2012.08.014.

The Outdoor Air Pollution and Brain Health Workshop

Michelle L. Block[*,1], **Alison Elder**[2], **Rick L. Auten**[3], **Staci D. Bilbo**[4], **Honglei Chen**[5], **Jiu-Chiuan Chen**[6], **Deborah A. Cory-Slechta**[2], **Daniel Costa**[7], **David Diaz-Sanchez**[8], **David C. Dorman**[9], **Diane Gold**[10], **Kimberly Gray**[11], **Hueiwang Anna Jeng**[12], **Joel D. Kaufman**[13], **Michael T. Kleinman**[14], **Annette Kirshner**[11], **Cindy Lawler**[11], **David S. Miller**[15], **Sri Nadadur**[11], **Beate Ritz**[16], **Erin O. Semmens**[17], **Leonardo H. Tonelli**[18], **Bellina Veronesi**[19], **Robert O. Wright**[20], and **Rosalind Wright**[20]

[1]Department of Anatomy and Neurobiology, Virginia Commonwealth University Medical Campus, Richmond, VA, USA

[2]Department of Environmental Medicine, University of Rochester, Rochester, NY USA

[3]Division of Neonatology, Department of Pediatrics, Duke University, Durham, NC, USA

[4]Department of Psychology and Neuroscience, Duke University, Durham, NC, USA

[5]Epidemiology Branch, National Institute of Environmental Health Sciences, Research Triangle Park, NC

[6]Department of Preventative Medicine, Keck School of Medicine, University of Southern California, Los Angeles CA, USA

[7]Office of Research and Development, United States Environmental Protection Agency, Research Triangle Park, NC

[8]Environmental Public Health Division, NHEERL, US Environmental Protection Agency, Research Triangle Park, NC

[9]Department of Molecular Biomedical Sciences, College of Veterinary Medicine, North Carolina State University, Raleigh, NC, USA

[10]Channing Laboratory, Department of Medicine, Brigham and Women's Hospital; and Harvard Medical School, Boston, MA, USA

[11]National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA

[12]School of Community and Environmental Health, College of Health Sciences, Old Dominion University, Norfolk, VA, USA

[13]Department of Environmental & Occupational Health Sciences, University of Washington, Seattle, WA, USA.

[14]Department of Medicine, University of California, Irvine, CA, USA

[*]**Address correspondence to:** Department of Anatomy & Neurobiology Virginia Commonwealth University Medical Campus Box 980709 Richmond, VA 23298-0709 **Phone:** (804) 827-1967 **Fax:** (804) 828-4977 .

CONFLICT OF INTEREST STATEMENT There authors declare that there are no conflicts of interest.

[15]Laboratory of Toxicology and Pharmacology, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, NC, USA

[16]Department of Epidemiology, Center for Occupational and Environmental Health, University of California, Los Angeles, CA, USA

[17]Department of Epidemiology, University of Washington, Seattle, WA, USA

[18]Mood and Anxiety Program (LT), Department of Psychiatry, University of Maryland School of Medicine, Baltimore, MD, USA.

[19]National Health and Environmental Effects Laboratory, Integrated Systems Toxicology Division, U.S. Environmental Protection Agency Research Triangle Park, NC, USA

[20]Preventive Medicine and Pediatrics, Mount Sinai School of Medicine, New York, NY, USA.

Abstract

Accumulating evidence suggests that outdoor air pollution may have a significant impact on central nervous system (CNS) health and disease. To address this issue, the National Institute of Environmental Health Sciences/National Institute of Health convened a panel of research scientists that was assigned the task of identifying research gaps and priority goals essential for advancing this growing field and addressing an emerging human health concern. Here, we review recent findings that have established the effects of inhaled air pollutants in the brain, explore the potential mechanisms driving these phenomena, and discuss the recommended research priorities/approaches that were identified by the panel.

Keywords

Air pollution; brain; particulate matter; ozone; central nervous system; susceptibility; epidemiology; neuroinflammation; neurotoxicity; behavior

INTRODUCTION

The association of air pollution with a number of adverse respiratory and cardiovascular health effects has been well documented. More recent epidemiological and animal toxicology studies have raised concerns about the potential impact of air pollution on central nervous system (CNS) outcomes including chronic brain inflammation, microglia activation, and white matter abnormalities leading to increased risk for autism spectrum disorders, lower IQ in children, neurodegenerative diseases (Parkinson's disease, PD; Alzheimer's disease, AD), multiple sclerosis, and stroke, as discussed below. Research needs to be pursued to gain comprehensive understanding of the contributions of perturbations in the brain due to the diverse particulate- and gas-phase components of air pollution mixtures. Alterations in the CNS may have direct health consequences or play a secondary role (s) by modulating the responses of the cardiovascular, pulmonary and immune systems. Conversely, alterations in the cardiovascular, pulmonary and immune systems due to air pollution may have effects on the brain due to the production of circulating pro-inflammatory mediators. Given the importance of understanding the effects of toxic exposure over the life span and evidence for the special vulnerability of the fetus, young children and the elderly to air pollution, the need for more research is obvious.

To evaluate how to support this emerging environmental health issue, the National Institute of Environmental Health Sciences (NIEHS) consulted with leaders in air pollution health effects research, behavioral neurotoxicologists, and basic neuroscientists studying the molecular and cellular basis of learning, cognition, and neurodegeneration. They were

charged with describing what is currently known so that NIEHS could then identify research priorities and gaps for future studies and recommend the most promising approaches for moving this nascent field forward.

While it is acknowledged that indoor air pollutants are likely to contribute to changes in brain health, the workshop focused on outdoor air pollutants. As such, this mini-review will discuss the following areas:

! ! The most likely components of outdoor air pollution responsible for adverse effects on the nervous system (e.g., particulate matter, polycyclic aromatic hydrocarbons (PAHs), black carbon, heavy metals, volatile organic compounds (VOCs), environmental tobacco smoke (ETS), ozone, carbon monoxide (CO).

! ! The potential cellular mechanisms by which inhaled outdoor pollutants compromise brain function (e.g., indirect effects of peripheral inflammation, changes in the blood brain barrier (BBB), direct neuronal and white matter injury).

! ! Experimental approaches (e.g., cell culture models, animal models, epidemiologic studies) that are best suited to address the effects of air pollution on the brain.

! ! Potential for neurotoxicity arising during periods of greatest vulnerability and from lifetime exposure.

1. OVERVIEW – OUTDOOR AIR POLLUTION AND CENTRAL NERVOUS SYSTEM DAMAGE/DISEASE

1.1 Outdoor Air Pollution and Human Health

Air Pollution Defined—Air pollution is a complex mixture that includes particulate matter (PM); ozone, carbon monoxide, sulfur oxides, nitrogen oxides, methane, and other gases, volatile organic compounds (e.g., benzene, toluene, and xylene), and metals (e.g., lead, manganese, vanadium, iron). It is derived from numerous natural and anthropogenic sources. The chemical composition of air pollution shows both spatial and temporal variations that reflect local sources (e.g., traffic character, industry, and natural biologic processes) and meteorological (including sunlight intensity) conditions. Although outdoor pollutants can penetrate the indoor environment, there are also unique sources of indoor air pollution from combustion (e.g., oil, gas, kerosene, coal, wood, and tobacco products), biologics (e.g., mite and cockroach fragments, molds), and vapors from building materials, furnishings, household cleaning and maintenance products. Importantly, several constituents of air pollution have the potential to reach the brain and adversely impact the CNS.

The PM component of air pollution is defined by its aerodynamic diameter (PM_{10}, <10 μm; $PM_{2.5}$ < 2.5 μm; ultrafine (UF), $PM_{0.1}$, < 0.1 μm). Inhaled particles are deposited differentially within the upper airways (nasopharynx, larynx), conducting airways, and alveolar region depending upon their aerodynamic size, airway anatomy, and ventilation pattern (Phalen et al. , 2010). The location where particles deposit can influence their rates of uptake by lung macrophages, their movement into the interstitium, and their potential translocation from the respiratory tract to other sites within the body, including the brain (Geiser et al. , 2005, Oberdorster et al. , 2004, Phalen, Mendez, 2010). Soluble components (e.g., metals, some organics) and very small particulate fragments or UF particles may also be absorbed through the respiratory tract surface into the systemic circulation. PM has received significant attention as a human health concern, where effects associated with PM include cardiopulmonary, cardiovascular, and more recently, CNS damage and disease.

Pulmonary and Cardiovascular Health Effects—There are substantial data showing that PM and other sources of air pollution are causally related to cardiovascular disease

(Brook et al. , 2010), can worsen asthma (Auerbach and Hernandez, 2012) especially in children (Breysse et al. , 2010, Patel et al. , 2011), and exacerbate chronic obstructive pulmonary disease (Eisner et al. , 2010). Epidemiological studies also demonstrate that exposure to ambient PM is associated with significantly higher risks of lung cancer mortality (mortality relative risk of 1.14 for a 10 $\mu g/m^3$ increase of $PM_{2.5}$) (Pope et al. , 2002). Accumulating evidence also indicates that the health effects of air pollution extend past the respiratory tract, resulting in cardiovascular damage and consequent elevation of morbidity and mortality (Brook, Rajagopalan, 2010).

Numerous studies in humans have demonstrated deleterious effects of air pollutant exposure on various measures of cardiovascular health (Gill et al. , 2011) including systemic inflammation (Peters et al. , 2001, Seaton et al. , 1999), blood pressure (Auchincloss et al. , 2008), heart rate variability (Liao et al. , 2004, Park et al. , 2010, Park et al. , 2005, Whitsel et al. , 2009), vascular function (Adar et al. , 2010, Diez Roux et al. , 2008), altered cardiac structure and function (Van Hee et al. , 2009, Van Hee et al. , 2010) and atherosclerosis (Diez Roux, Auchincloss, 2008, Kaufman, 2010). Investigations of these cardiovascular disease endpoints in population-based studies and in studies of sensitive subgroups have enhanced our understanding of the mechanistic pathways underlying associations between air pollutants and cardiovascular morbidity and mortality. The three broad pathways that have been identified include: (1) the release of inflammatory and oxidative stress mediators by the lungs into the systemic circulation; (2) interactions between pollutants and pulmonary neuronal afferents resulting in autonomic imbalance; and (3) direct translocation of particle constituents or particles from the respiratory tract into the systemic circulation. It is hypothesized that these same mechanisms underlying the effects of air pollution on pulmonary and cardiovascular health may also mediate responses in the brain.

1.2 Outdoor Air Pollution and the Brain

Increasing evidence links air pollution to CNS diseases, behavior deficits, neuroinflammation, and neuropathology in human and animal studies (Block and Calderon-Garciduenas, 2009, Lucchini et al. , 2011). However, the underlying mechanisms and sequence of events that culminate in neurotoxicity remain poorly understood. Consistent with prior air pollution toxicology research, pre-existing disease conditions, age, and critical periods of development may modulate CNS effects, but at the present time, few studies have systematically explored these issues. Here, we summarize the current findings of what is known about air pollution effects in the brain and highlight potential mechanisms.

Human Reports—While the majority of prior studies have focused on the effects of air pollution in cardiovascular and pulmonary disease, evidence now points to a potential role for air pollution in CNS disease (Block and Calderon-Garciduenas, 2009). In fact, postmortem sampling has identified PM in the human brain, albeit of unknown composition and origin (Calderon-Garciduenas et al. , 2008b). In a small controlled-exposure study utilizing a blinded randomized crossover design, a significant relationship was observed between exposure to high levels of diesel exhaust and increased brain (frontal cortex) activity as measured by quantitative electroencephalography (Cruts et al. , 2008). Importantly, human studies have also shown that living in conditions with elevated air pollution is linked to decreased cognitive function (Calderon-Garciduenas et al. , 2008a, Chen and Schwartz, 2009, Power et al. , 2011, Ranft et al. , 2009, Suglia et al. , 2008, Weuve et al. , 2012), lower neurobehavioral testing scores in children (Wang et al. , 2009), a decline in neuropsychological development in the first 4 years of life (Morales et al. , 2009), AD- and PD- like neuropathology (Calderon-Garciduenas et al. , 2010, Calderon-Garciduenas et al. , 2012, Calderon-Garciduenas et al. , 2004, Morales, Julvez, 2009), increased stroke incidence (Mateen and Brook, 2011) (Donnan et al. , 1989, Henrotin et al. ,

2007, Villeneuve et al. , 2006), and elevated autism risk (Volk et al. , 2011). Some air pollution components such as manganese have been associated with CNS pathology, as elevated levels of manganese in the air have been shown to correlate with enhanced PD risk (Finkelstein and Jerrett, 2007)

Neuroinflammation and Air Pollution: A Central Role for Microglia—Recent reports reveal that controlled inhalation exposure to ambient PM (Campbell et al. , 2009, Campbell et al. , 2005), ozone (Santiago-Lopez et al. , 2010), diesel exhaust (Gerlofs-Nijland et al. , 2010, Levesque et al. , 2011a, Levesque et al. , 2011b), and manganese (Antonini et al. , 2009, Elder et al. , 2006) results in elevated cytokine expression and oxidative stress in the brain. At present, the mechanisms responsible for the initiation of neuroinflammation in response to air pollution are poorly understood and may be exposure-specific. One theory implicates activated brain microglia in neuroinflammation.

Microglia are the resident innate immune cells in the brain and are predominant regulators of neuroinflammation, evidenced by their production of pro-inflammatory (e.g., Interleukin-1! , tumor necrosis factor (TNF)-α, prostaglandin E_2, and interferon-γ) and reactive oxygen species (e.g., $^{\bullet}NO$, H_2O_2, $O^{\bullet}{}_2^-$, and $ONOO^-$/ONOOH) (Block et al. , 2007). Although microglia are necessary for normal brain function, excessive and chronic activation can result in neurotoxicity, such as the initiation and/or amplification of neuronal damage (Block and Hong, 2005). Importantly, microglia are activated in neurodegenerative diseases, as indicated by analysis of postmortem brains from AD and PD patients (McGeer et al. , 1988), and have been implicated in the progressive nature of each disease (Block and Hong, 2005, 2007, Lull and Block, 2010, McGeer and McGeer, 2010). Microglia are also activated in the pre-frontal cortex of autistic children (Morgan et al. , 2010) and in response to ischemic stroke (Yenari et al. , 2010). *In vitro* studies have shown that PM activates microglia, amplifies the microglial response to pro-inflammatory stimuli, and causes cellular damage (Block et al. , 2004, Morgan et al. , 2011, Sama et al. , 2007). This is in concert with additional in vitro studies showing that PM activates macrophages through a toll-like receptor (TLR) 2 and 4-dependent mechanism (Shoenfelt et al. , 2009). Microglia are known to express many pattern recognition receptors, including TLRs, where TLR's initiate a cascade of inflammatory responses that are dependent on the activation of TLR's pathways (Lehnardt, 2010). Furthermore, dopaminergic neurons underwent cell death only in the presence of microglia following nanometer-sized diesel exhaust particle exposure (Block, Wu, 2004), suggesting that this cell type may be important for neurotoxicity.

Consistent with human studies (Calderon-Garciduenas, Solt, 2008b), recent reports have demonstrated in rodent models that air pollution activates microglia (Levesque, Taetzsch, 2011b, Morgan, Davis, 2011). In rodents exposed to diesel exhaust via inhalation, measures of neuroinflammation were reported to be the highest in brain regions with the most microglia (Levesque, Taetzsch, 2011b) . Pro-inflammatory markers have also been shown to correlate with manganese translocation along the olfactory neuronal pathway (Elder, Gelein, 2006). These studies suggest that specific brain region vulnerability is likely a combination of the cellular architecture of the region (e.g., microglia density), the characteristics of the exposure in question, and the route of administration. These studies support the hypothesis that air pollution may be a common and continuous environmental source of microglial activation.

Other CNS cells are also predicted to be affected by air pollution exposure. For example, astrocytes are the most prevalent cell type in the brain and are reported to be activated in humans (Calderon-Garciduenas, Mora-Tiscareno, 2008a) and animals (Elder, Gelein, 2006) following exposure to certain air pollutants. Oligodendrocytes exist in the brain as both progenitor cells that can produce cytokines and growth factors (Hahn et al. , 2010) and

mature cells that insulate neurons (Mekhail et al. , 2012). While oligodendrocytes have been largely overlooked in air pollution research, it is likely that these cells are affected in children (Calderon-Garciduenas, Mora-Tiscareno, 2008a) and dogs (Calderon-Garciduenas et al. , 2002) with air pollution-induced white matter lesions. Finally, neurons themselves can be affected by air pollution directly, a possibility suggested by their ability to internalize PM (Calderon-Garciduenas, Solt, 2008b), and are also likely damaged in white matter lesions in humans (Calderon-Garciduenas, Mora-Tiscareno, 2008a). Furthermore, neuronal damage may also contribute to the pro-inflammatory milieu in the brain (Block, Zecca, 2007).

Air Pollution and Neurodegenerative Disease Proteins—Changes in α-synuclein (Chahine and Stern, 2011, Shi et al. , 2011), Aβ42 (Perrin et al. , 2011), and tau (Perrin, Craig-Schapiro, 2011) have been proposed as potential indicators of preclinical neurodegenerative diseases, such as PD, AD, and frontotemporal dementia. Neuropathological analyses of post-mortem tissues from humans living in highly polluted areas have shown elevations in Aβ42 (Calderon-Garciduenas, Kavanaugh, 2012, Calderon-Garciduenas, Solt, 2008b), hyper-phosphorylated tau (Calderon-Garciduenas, Kavanaugh, 2012), and α synuclein (Calderon-Garciduenas, Solt, 2008b). Importantly, these findings have been confirmed in animal studies using subchronic (6 months) inhalation exposures to DE, demonstrating that Aβ42, phosphorylated tau, and α synuclein are elevated in rat brain (Levesque, Surace, 2011a). Together, these findings suggest that exposure to air pollution has the potential to impact neurodegenerative disease pathways. However, at this time epidemiology data are unavailable and the ability of the complex mixture of air pollution to damage neurons, either directly or through inflammation is poorly understood.

Outdoor Air Pollution and Behavior—There is increasing evidence that air pollution has neuropsychological effects in humans and in animal models (Guxens and Sunyer, 2012). Several experimental studies have linked air pollution to neurochemical changes (Suzuki et al. , 2010, Yokota et al. , 2009) and markers of synaptic plasticity (Win-Shwe et al. , 2009, Win-Shwe et al. , 2011) that may precede or be independent of overt neuronal death. Animal experiments provided evidence that diesel exhaust inhalation decreases measures of spatial learning (Win-Shwe, Yamamoto, 2011), motor behavior (Suzuki, Oshio, 2010, Yokota, Mizuo, 2009), and even impacts behavioral measures of emotion (Yokota et al. , 2011). Exposure to near roadway air pollution in mice for 10 months has also been linked to decreases in spatial learning and depressive behavior (Fonken et al. , 2011). While the mechanisms driving these phenomena are unclear, these studies emphasize that there are clear behavioral effects associated with air pollution exposure, supporting a potential link to human disease.

The Chemical Complexity of Air Pollution-induced Neurotoxicity—While air pollution is a complex mixture that likely affects human health through multiple pathways, some of the individual constituents or characteristics of specific components have already been implicated in neurotoxicity and nervous system disease independently. Oberdörster and Utell (Oberdorster and Utell, 2002) first proposed that the brain may be vulnerable to ultrafine ambient PM. It was further shown that model nanosized particles could cross the BBB and physically enter the CNS of animals (Lockman et al. , 2004). Biological components of PM such as endotoxins, mold, and pollen have been associated with neurodevelopmental disorders (e.g., schizophrenia, autism, mental retardation) and neurodegenerative diseases (e.g., AD, PD) (Meyer et al. , 2009). A major biological inflammatory component of PM is endotoxin. In fact, it has been shown that the “activation” properties and cytokine production of PM is directly related to the content of endotoxin (Shoenfelt, Mitkus, 2009). Short term exposure to endotoxins such as bacterial

lipopolysaccharides administered intranasally in rats induces cytokine expression in several brain regions, activates the stress axis and alters behavioral coping responses to stress mimicking all the effects of long term exposure to PM (Tonelli et al. , 2008). In addition, metals, solvents, and PAHs found in air pollution and carried on PM have been associated with neurodegenerative diseases (e.g., PD, AD) (Budimir, 2011, Hozumi et al. , 2011, Meloni and Vasak, 2011, Wirdefeldt et al. , 2011) and cognitive deficit disorders (Edwards et al. , 2010, Freire et al. , 2010, Pearce and Braverman, 2009).

Lead and manganese are strongly implicated in neuronal damage and CNS disease. The clinical manifestation of lead neurotoxicity includes impaired intellectual function and attention, encephalopathy, and convulsions (Mendola et al. , 2002). Neurotoxicity associated with the organic solvents such as toluene has also been reported occupationally and in experimental settings (Win-Shwe and Fujimaki, 2010). More specifically, toluene exposure is clinically associated with frequent headaches, memory impairments, and CNS depression, among other effects (Win-Shwe and Fujimaki, 2010). Manganese exposure produces a form of parkinsonism with bradykinesia, rigidity, and occasional resting tremor (Lucchini et al. , 2009). Willis and coworkers (2010) have recently reported that the incidence of PD is greater in urban U.S. counties with high industrial release levels of copper or manganese (Willis et al. , 2010). Similarly, some investigators have suggested that exposure to manganese and other welding fumes could predispose individuals to earlier onset PD (Racette et al. , 2001). In addition, various air pollutants, such as PAHs, can cause damage to the sensory neurons present in the olfactory epithelium and associated functional changes (Feron et al. , 2001, Tonelli and Postolache, 2010, Upadhyay and Holbrook, 2004). Interestingly, olfactory damage and loss of smell are commonly seen in both PD and AD (Tonelli and Postolache, 2010).

It is important to note that short inhalation exposures (1 month) to some forms of complex air pollution mixtures such as diesel exhaust (Levesque, Taetzsch, 2011b) and concentrated urban air pollution (Veronesi et al. , 2005) fail to cause neurotoxicity in healthy, young adult animals. On the other hand, short term ozone exposure in rodents has been reported to result in cerebral edema (Cretu et al. , 2010), neurodegeneration in the hippocampus, striatum, and substantia nigra (Pereyra-Munoz et al. , 2006, Rivas-Arancibia et al. , 2010, Santiago-Lopez, Bautista-Martinez, 2010), and altered behavior (Rivas-Arancibia et al. , 2003, Santucci et al. , 2006, Sorace et al. , 2001). Further, exposure to carbon monoxide in animals has been associated with increased oxidative stress in cochlear blood vessels, damage to spiral ganglia neurons, inner hair cells(Lopez et al. , 2008) and ultimately with hearing loss (Schwela et al. , 2005). Thus, the potential neurotoxic effects of air pollution are likely to be exposure specific, time-dependent and dose-dependent, emphasizing the importance of employing accurate occupational and ambient exposure models in future studies.

Shared Mechanisms of CNS Susceptibility and Cardiotoxicity—Subclinical and clinical cardiovascular disease are established risk factors for cognitive decline and dementia (O'Brien, 2006, Stampfer, 2006), and it is likely that the observed impact of air pollutants on the brain occurs, at least in part, downstream of air pollution-induced cardiovascular effects. It is also plausible that the generalized mechanistic pathways described by Brook *et al.* (Brook, Rajagopalan, 2010) act independently of cardiovascular effects. Circulating cytokines, markers of systemic inflammation, have been shown to result in neuroinflammation (Rivest et al. , 2000) and neurotoxicity (Qin et al. , 2007) and to exacerbate neurodegenerative progression (Perry et al. , 2007). Moreover, it has been implicated that systemically circulating ultrafine particulate matter can reach the brain causing inflammation and oxidative stress (Block and Calderon-Garciduenas, 2009, Peters et al. , 2006). Potential mediators of these effects are astroglia, cells important in maintaining the BBB and the regulation of neurotransmitter uptake and response to injury, and microglia,

the immune cells of the brain (Block and Calderon-Garciduenas, 2009). In addition, the pathways that confer cardiovascular risk by way of the autonomic nervous system(Liao, Duan, 2004, Park, O'Neill, 2005, Whitsel, Quibrera, 2009) imply that air pollutants exert direct quantifiable effects on preganglionic neuronal activity. Thus, cardiovascular disease and air pollution may also interact to influence CNS health.

1.3 Initiating Events in Air Pollution-Induced Effects in Brain

Direct Transport via the Olfactory Epithelium—The nasal cavity provides an alternative transport pathway for direct brain delivery of some inhaled materials via olfactory neurons into the olfactory bulbs. Further CNS distribution can then occur to the piriform cortex, olfactory tubercule, amygdala and entorhinal cortex (Lucchini, Dorman, 2011). Further, anterograde pathways are proposed to connect from these regions to the orbito-frontal cortex, thalamus, hypothalamus and hippocampal formation (Sunderman, 2001b). Reports indicate that ultrafine PM deposited on the olfactory epithelium can indeed distribute throughout the brain as a result of olfactory transport (Elder, Gelein, 2006, Oberdorster et al. , 2009, Oberdorster, Sharp, 2004). Various metal compounds (manganese, iron, cadmium, thallium, mercury, cobalt, zinc) as well as carbon particles appear to move into brain following inhalation or intranasal/tracheal instillation exposures (Sunderman, 2001b). However, not all studies confirm these transport routes (Rao et al. , 2003) and movement is influenced by the chemical species. Mechanisms by which such transport occurs remain unknown although roles for metal-binding carrier molecules or transporter proteins in facilitating the olfactory nerve transport of solutes have been proposed (Genter et al. , 2009, Sunderman, 2001a). It should also be noted that animal species differences are important since the relative surface area of the nasal olfactory mucosa in humans (5%) is much smaller than that of rodents (50%)(Dorman et al. , 2002).

A direct "nose-to-brain" transport of manganese has been demonstrated by several investigators. The presence of manganese (as ^{54}Mn) in the olfactory bulb of rats, mice, and freshwater pike on the side ipsilateral to the instilled nostril (Tjalve and Henriksson, 1999) were demonstrated after intranasal instillation of radiolabeled manganese chloride. Olfactory transport of inhaled Mn has also been shown (Dorman, Brenneman, 2002) in an animal model in which one nostril was occluded, thus restricting olfactory transport of Mn to the side of the rat brain ipsilateral to the patent nostril. In these studies, direct delivery along the olfactory route accounted for nearly all of the ^{54}Mn found in the olfactory bulb and tract of the rat brain following acute Mn inhalation, indicating that Mn can cross synapses within the olfactory pathway and travel via secondary and tertiary neurons to more distal sites within the brain. Lewis and coworkers (2005) reported that the rat trigeminal nerve may also translocate Mn from the nasal cavity (Lewis et al. , 2005). Although olfactory transport rapidly delivers Mn to brain structures in the olfactory pathway, the trigeminal route appears to be relatively slow (and perhaps inefficient) in delivering inhaled Mn to the rat striatum and other more distant brain structures (Leavens et al. , 2007).

Traversing Metabolic Barriers in the Olfactory Epithelium—Neuroepithelial damage and biotransformation of ambient air pollutants may also impact bioavailability in the brain and consequent CNS effects. The epithelium of olfactory mucosa has high activity and expression of cytochrome P450 (CYP) isoforms including CYP1A2, 2 A, 2B, 2E, and 2G (Livertoux et al. , 1996, Longo et al. , 2000, Voigt et al. , 1993). These phase 1 enzymes catalyze the biotransformation of ambient air pollutants such as polycyclic aromatic hydrocarbons, semi-quinones and quinones into toxic metabolites, such as mutagenic epoxide or reactive oxygen species. The presence and activity of flavin-contamining monooxygenase in olfactory epithelium also produces deleterious reactive metabolites from air pollutants (Genter et al. , 1995). Importantly, phase II enzymes in the nasal cavity

epithelium, such as UFP-glucuronosyltransferase, epoxide hydrolase, sulfotransferases, and glutathione S-transferases (Bond et al. , 1988),function to detoxify reactive metabolites formed by CYP-dependent activities. Thus, the appropriate balance of phase I and II enzymes in the epithelium of olfactory mucosa may provide a first line of defense for the brain, limiting axonal transport of ambient air pollutants and toxic metabolites from the olfactory nerve cells to the olfactory bulb. However, while the level and activity of CYP enzymes in the brain are low when compared to those in the nasal mucosa (Ghersi-Egea et al. , 1988), it has been proposed that air pollutants escaping the metabolic barrier of the olfactory epithelium may reach the brain and undergo local cerebral metabolism which could have deleterious CNS effects (Minn et al. , 2002). In fact, a recent study demonstrated that aged mice failed to upregulate phase II enzymes in the brain in response to nanoparticle urban air pollution exposure (Zhang et al. , 2012), offering some insight into the role of aging on CNS effects. Clearly, there is a need for more research to sort out these biological and chemical factors that may contribute to the potential for nasal or other transport of air pollution to the brain.

Systemic Transport via the Blood Brain Barrier—Systemically delivered ultrafine PM or its bioavailable components may enter the brain through the BBB. The BBB itself comprises multiple cell types (e.g., endothelia, pericytes, astrocytes) and transporter systems which together provide an “impermeable” barrier covering most regions of the brain and spinal cord. When intact and not impaired by disease, age, infection, or toxicants, the BBB effectively protects the CNS interstitium from macromolecules, toxins, and small organic drugs (Miller, 2010). Recent evidence indicates that air pollutants have been shown to alter BBB function. For example, aluminum nanoparticles have been reported to injure endothelial cells and damage the BBB (Chen et al. , 2008). Human exposure to air pollution shows endothelial cell damage in the cerebral vasculature, with increases in ICAM and VCAM present (Calderon-Garciduenas, Solt, 2008b). In addition, *in vitro* studies using whole brain rat capillaries reveal that treatment with particulate matter causes production of cytokines and reactive oxygen species, which signal changes in transporter expression and function (e.g. P-glycoprotein and Multidrug Resistance Associated Protein-2) and a decrease in expression of various tight junction proteins (Hartz et al. , 2008). Thus, brain capillaries respond to air pollution components by regulating the physical and chemical barrier function and producing pro-inflammatory signals. In addition, this response may serve as a pro-inflammatory sensor (Hartz, Bauer, 2008) and ultimately distribute reactive oxygen species, cytokines, and particulate matter to the brain parenchyma, further contributing to CNS pathology.

There are distinct brain regions (e.g., median eminence, area postrema, subfornical organ and periventricular regions of the hypothalamus) in which the BBB is comprised of a more fenestrated endothelial layer (Abbott et al. , 2010). Perivascular microglia use their proximity to this “leaky” barrier structure to survey the systemic environment for adverse stimuli such as inflammatory cytokines, and possibly soluble or particulate pollutants that have exited the respiratory tract and entered the systemic circulation. The perivascular microglia are activated through innate immune pathways in an inflammatory cascade that includes NF-κB activation and up-regulation of numerous surface molecules such as major histocompatibility complex (MHC) and various receptors (e.g., Toll-like MAC-1, CD14, chemokines) (Carrillo-Esper, 2003). These microglia subsequently release free radicals and pro-inflammatory cytokines (interleukin-1β, TNF-α) that can damage surrounding neurons. These events represent a common pathway for microglia-mediated neurodegeneration (Block and Hong, 2005).

The latter scenario suggests that physical entry of soluble or particulate pollutants into the brain may be unnecessary to stimulate adverse changes. It further indicates that the

inflammatory mediators released by pollutant inflamed organ systems such as the respiratory tract or gut can trigger the microglia located along the fenestrated BBB (Finnerty et al. , 2007, Hetland et al. , 2005, Nel, 2005, Soukup and Becker, 2001). This peripheral inflammation results in the systemic release of inflammatory mediators (e.g., cytokines) over time that can then activate the brain's immune surveillance cells (i.e., microglia) (Carrillo-Esper, 2003) and alter CNS immune response, function, and/or behavior (Perry, Cunningham, 2007, Tonelli and Postolache, 2010). At this time, the role of the peripheral immune response in the CNS effects of air pollution has not been tested.

Sensory Afferent Signaling—An additional potential route of entry for air pollutants is via the sensory afferents found in the gastrointestinal tract as part of the brain-gut axis (Perry, 2004). It is known that PM particulates that are too large to enter the lungs are quickly cleared by swallowing (Mutlu et al. , 2011). Likewise, clearance of particles that deposit in the deep lung eventually occurs via the mucociliary escalator and, so, gastrointestinal tract exposure cannot be discounted. The sensory afferents of the dorsal vagus nerve located in the gut communicate directly with brain stem neurons. It is interesting to note that abnormalities in olfaction-vagal-brainstem routes (gastric systems secondary to swallowing of nasal secretions in saliva) have been studied as the early pathologies of Parkinson's neurodegeneration (Hawkes et al. , 2007, Jang et al. , 2009). Pulmonary afferents from the airways (Hunter and Dey, 1998, Hunter and Undem, 1999) and/or deep lung may also represent an additional target site.

1.4 Susceptibility to Air Pollution

Interactions between Toxicants and Stress—Psychosocial stress and toxicants such as air pollutants are known to influence common physiological pathways including neuroendocrine and autonomic function, oxidative stress and proinflammatory immune pathways (Dantzer et al. , 2008, Tomei et al. , 2003). Therefore, the interaction between these factors is complex and likely bi-directional in which stress may influence the negative outcomes of exposure to air pollution and exposure to air pollution may also lead to maladaptive coping responses to stress. For example, an correlation between stress (community violence) and ambient air pollution (measured as NO_2) has been reported for urban childhood asthma risk (Clougherty et al. , 2007) suggesting that stress exacerbates the effects of air pollution on respiratory illness. Furthermore, increased asthma risk has been correlated with poorer socioeconomic status (Drake et al. , 2008). Given that social stress tends to track along socio-economic gradients, poor communities may be at greatest risk for the toxicity of ambient air pollutants due in part to higher levels of psychosocial stress. Conversely, socially enriched environments may protect children from the toxic effects of environmental hazards (Laviola et al. , 2008, Schneider et al. , 2001). On the other side, higher perceived stress on poorer cognitive function have been reported in elderly men and the effect has been shown dependent on low-level lead exposure (Peters et al. , 2010). Animal studies have shown that intranasal instillations of bacterial lipopolysaccharides (LPS) are capable of inducing depressive-like behavior and increased hormonal responses to stress (Tonelli et al, 2009). Both lead and LPS are common components of air pollution with the potential of significantly impact on stress responsiveness. An integrated approach that addresses both cleaner air and social interventions may have significant implications for prevention and intervention in high-risk urban populations (O'Neill et al. , 2003, O'Neill et al. , 2008, Wright, 2006). In sum, understanding potential interactions between ambient air pollution and psychosocial stress promises a more complete understanding of the toxicity of air pollutants at both individual and population level.

Neurotoxicity, the Environment and Susceptibility: The Role of Timing—Regardless of whether one studies genetic, social or even nutritional susceptibility, besides

exposure and disease, there is always a third dimension when considering environmental exposures: timing. Dose-response curves are not likely to be constant across all life stages. Fetal life and early childhood, in particular, are times of vulnerability. These life stages are periods of rapid growth, cell differentiation, organogenesis and, in the case of the brain, network development. Relatively small disruptions in these processes may set individuals on trajectories that have subtle effects in early years and profound effects later in life.

Because many genes are only expressed during specific developmental stages and are subsequently turned off, gene-environment interactions may be partly or even largely dependent on the timing of the environmental exposure. Such interactions likely depend on the life stage at which exposure occurs. For example, growing evidence from animal research indicates that the CNS is highly vulnerable to chemical injury during development (Faustman et al. , 2000, Rodier, 2004). This is due to interference with processes critical to neurodevelopment such as neuronal growth, synaptic network formation, neuronal migration, and development of receptor numbers. These processes are most active during fetal life and in childhood and subside during adult life. If toxic exposures impact these growth and differentiation processes, they could alter the trajectory of brain development, but the same chemical would be less toxic once development is complete. Differential toxicity in children vs. adults has been shown for many chemicals including methyl mercury (Amin-Zaki et al. , 1974, Marsh et al. , 1980), PCBs (Tilson et al. , 1990), organophosphate pesticides (Engel et al. , 2007), and lead (Bellinger et al. , 1987, Schnaas et al. , 2006). With respect to environmental effects that act via gene-environment interactions, effects may be dependent primarily on whether exposure timing corresponds to a critical developmental window during which the gene is highly expressed. A design that cannot address the timing of environmental exposures would likely miss such gene-environment interactions (Tsuang et al. , 2001). Likewise, interactions that also involve other risk factors - social, nutritional, etc,-may depend on the timing of the joint exposure for similar reasons.

Aging—Many neurodegenerative diseases are predicted to be the result of cumulative exposures across an entire lifetime (Carvey et al. , 2006) and aging is a well-known risk factor for the two most prevalent neurodegenerative diseases, AD and PD (von Bernhardi et al. , 2010). Further, aging is linked to elevated neuroinflammation, where aged brains show an elevation of cytokines and microglial activation (Sparkman and Johnson, 2008, von Bernhardi, Tichauer, 2010). In addition, aged brains are more vulnerable to environmental insult, particularly pro-inflammatory stimuli (Sparkman and Johnson, 2008, von Bernhardi, Tichauer, 2010), which may be of importance given the extensive reports of a pro-inflammatory response in the brain with diverse forms of air pollution exposure (Block and Calderon-Garciduenas, 2009). Notably, aging may be especially important to inflammation-mediated neurotoxicity in response to peripheral inflammation, e.g. chronic neuroinflammation in response to a single intraperitoneal injection of lipopolysaccharide – a potent inflammatory stimulus – in young adult mice will only culminate in dopaminergic neurotoxicity in aged animals (Qin, Wu, 2007). Further, aged individuals are more vulnerable to the cardiopulmonary health effects of air pollution (Namdeo et al. , 2011). For example, acquired immunity declines with age in the respiratory system (Busse and Mathur, 2010), which has the potential to negatively impact the brain. However, the effect of the interplay of air pollution and aging on CNS health is largely unknown.

Gene-environment Interactions—Genetic factors may be modifiers of chemical neurotoxicants. The current state of art for gene-environment interaction is to conduct genome wide screening in a discovery stage to generate a candidate gene list for second stage genotyping in an independent sample. The subset of single nucleotide polymorphisms (SNPs) that are significant in the discovery stage are tested in an independent population to validate the findings. A smaller subset in this second stage are expected to be significant,

and more likely contain any true positive results. The alternative design is to conduct a biological pathway study, also known as a candidate gene approach. This is less costly and is hypothesis driven, unlike the genomic approach. Typically, investigators select candidate genes which reflect the biological pathways implicated in air pollution toxicity. Examples might include inflammation (IL-6, inducible nitric oxide synthase (iNOS), TNF-α),(Castro-Giner et al. , 2009, Thompson et al. , 2010, Thomson et al. , 2007) the autonomic system (Norepinephrine transport, NET [HUGO name SLC6A2]) (Min et al. , 2009), and HPA axis (glucocorticoid receptor (GCR) [HUGO name NR3C1]and 11- β hydroxysteroid dehydrogenase-2(11-β HSD2) [HUGO-HSD11B2])(Derijk, 2009, Derijk et al. , 2002, Zaehner et al. , 2000). There is no methodology that can comprehensively create a complete list of candidate genes. The potential list of candidate genes is likely impossible to comprehensively select a priori, as genes may play roles in chemical metabolism, cellular toxicity, neurotransmitter metabolism, or could even work indirectly (i.e., disrupt the metabolism of a nutrient involved in brain function). The selection of candidate genes is therefore subjective and will vary from investigator to investigator. This is the major limitation of this approach. In addition, it is unlikely that all the relevant genes and regulatory regions that modify the toxicity of ambient pollution are even known. Thus, a candidate gene approach can never comprehensively interrogate all the potential genetic modifiers of environmental toxicants. The genomic approach might require a much larger sample and may be most feasible in the context of pooled studies or multi-center collaborations. A further complication is that gene-environment interactions could be manifest in a brain region-specific manner, thus requiring careful tissue harvesting to ensure that target areas are not lost of that a signal of interest is not diluted. However, the possibility exists that extremely large gene-environment interaction effects have not yet been discovered, given the paucity of research on such interactions in genomics. If such effects do exists, large sample sizes may not be necessary.

Epigenetics—Variation in DNA sequence cannot explain all host susceptibility to ambient pollution. Indeed, phenomena such as fetal programming are difficult to explain in the context of DNA sequence variation. The toxicity of air pollutants is undoubtedly multifactorial, and one potential pathway yet to be fully explored is epigenetics, the study of changes in gene function that are mitotically and/or meiotically heritable and that do not entail a change in DNA sequence (Wu and Morris, 2001). DNA methylation is the best studied of the epigenetic processes that regulate gene silencing and there is a growing body of evidence demonstrating an association between DNA methylation and environmental ambient pollutants (Baccarelli et al. , 2009). DNA methylation changes can occur in somatic tissues during any stage of development and program gene expression changes. Importantly, DNA methylation has been linked to brain development. For example, failure of DNA methylation systems leads to clinical syndromes including mental retardation and autistic-like behaviors (Shahbazian and Zoghbi, 2002), and DNA methylation changes have been linked to other behavioral disorders as well (Levenson et al. , 2006, Petronis, 2003). Furthermore, animal studies increasingly demonstrate that environmental factors can alter DNA methylation patterns and that these changes correlate with animal behavior (Weaver et al. , 2004, Weaver et al. , 2001). Epigenetic modifications of regulatory DNA sequences in response to variations in environmental conditions can be a critical source of variation in gene expression and function. In addition, DNA methylation changes can mediate the relationship between genome and environment throughout each stage of neurodevelopment, including fetal life. Thus, while the role of epigenetics in CNS vulnerability to air pollution has yet to be explored, this area of research may be of significant importance.

1.5 Design and Conduct of Epidemiologic Studies on Ambient Air Pollution and Brain Health

There is significant need for well-designed studies investigating the human risk for CNS disease with air pollution exposure. There are several methodological challenges as related to confounding, exposure misclassification, and other potential biases that are unique to conducting epidemiologic research. In the context of studying air pollution and brain health, confounds are proximate causes (or antecedent predictors) of both air pollution exposure and the disease outcomes. For example, maternal mental health status may be a potential confounder in the putative associations of behavioral problems in children and prenatal exposure to air pollution, because the increased risk of various adverse neurobehavioral outcomes in offspring (either through genetic predisposition or not) are associated with mothers' mental health status, which may affect residential choice and thus determine the estimated residential exposures to ambient air pollution during pregnancy or early childhood. Or if older people with better cognitive function behave differently (e.g., move to neighborhoods with cleaner air) from those with poor brain health, this may lead the appearance of a spurious positive association between air pollution and cognitive decline. Epidemiologic studies of the effects of long-term air pollution exposures on brain health thus have to be designed carefully and be able to address the methodological issues related to exposures and confounders likely to vary over time.

Comorbidities—PM may affect those with pre-existing neurological disease as it may affect disease progression rather than or in addition to initiation. Oxidative stress is posited as a possible mechanism that mediates air pollution induced adverse effects on brain health. Therefore, comborbidities with other non-neurological diseases where there may have been underlying increases in oxidative stress (e.g. cardiovascular diseases, heart failure, diabetes, lupus, and obesity) need to be carefully assessed because of their resulting possibly greater susceptibility to the adverse effects on human brains. If particles escape the respiratory tract(Oberdorster, Elder, 2009) and enter the vasculature, those individuals with diseases that promote increased airway particle deposition may be at increased risk; this includes those with mild asthma and COPD(Pope, 2000). In those with more severe asthma, the increased particle deposition is probably counterbalanced by increased mucus production that will limit particle migration to the periphery. This will be an important consideration in future studies.

Exposure Assessment for Ambient Air Pollution—Most ambient (outdoor) air pollution studies often conducted in large human populations base their exposure assessment on routine nationwide monitoring networks for "criteria" air pollutants that measure all or some of the gases NOx, CO, ozone, SO_2, as well as particles (lead and PM_{10}, and more recently also $PM_{2.5}$). These pollutants commonly originate from the same source (e.g., CO and NO_x from motor vehicles; sulfate particles and SO_2 from power plants and industrial facilities) and even interact with each other chemically. As the ambient levels of these pollutants are correlated in space and time, it is hard to disentangle biologic effects of individual pollutants in air pollution epidemiologic studies with exposure assessment that solely relies on environmental monitoring network data. The relative importance of different ambient air pollutants in producing health effects may vary by endpoint (stroke/ neurodegeneration) and pollutants in mixtures may act synergistically. For pollutants that are more spatially homogenous (e.g., $PM_{2.5}$), monitors placed in urban areas allow estimation of community-wide average exposures and record variation over time very well but these networks are often inadequately dense for spatially heterogeneous pollutants where proximity to sources determines peak exposures; e.g., ultrafine particles (<0.1 μm), black smoke (a marker of exhaust particles), CO and NOx/NO/NO2 as markers of vehicle exhaust

have been shown to decrease exponentially with distance (within hundreds of feet) from freeways (Zhou and Levy, 2007, Zhu et al. , 2002a, Zhu et al. , 2002b).

Lack of sufficient exposure characterization to inform the possible sources of pollutant exposures is another limitation of epidemiologic studies that rely only on air monitoring network to assess the exposures. Recently some health effect studies employed simple measures of proximity to sources such as traffic or much more complex models such as land use based (LUR) regression and emissions based models (such as CALINE4). For example, to characterize traffic-related air pollutants in urban environments, LUR models are based on simultaneous measurements of vehicle exhaust markers, such as NO_x, taken at many locations throughout an urban area during multiple two-week periods (e.g. see Su et al 2009) (Su et al. , 2009). Various geographic information systems (GIS) parameters (e.g. traffic and roadway density, traffic volumes, truck routes, population density, and land use features and sometimes even satellite-derived data such as soil brightness) are used to predict the measured concentrations (Sahsuvaroglu et al. , 2006). This fine scale spatial model can then be used to estimate exposure concentrations at specific locations based on the GIS parameter values. Also, much more computationally intense air dispersion models have been developed based on vehicle emission factors such as the CALINE4 model that relies on for example the California Air Resources Board's EMFAC2007 model (http://www.arb.ca.gov/msei/onroad/latest_version.htm), paved road-dust emissions for $PM_{2.5}$ based on in-roadway measurements (Fitz and Bufalino, 2002) and meteorological factors (hourly wind speed, direction, and temperature from the National Weather Service and average mixing heights) to derive pollutants concentrations for particles or gases (Benson, 1989, Croes and Fujita, 2003, Wu et al. , 2009a, Wu et al. , 2005, Wu et al. , 2009b). The performance of such LUR or emissions based models in health effects studies; however, still needs to be further explored and depends on whether or not the data sources indeed can accurately model exposures in time and space. The accuracy and precision of exposure prediction based on LUR may vary by geographic areas in which these models are employed (Wu et al. , 2011).

In contrast to the population-monitoring networks described above, short term personal monitoring and biomarkers promise in-depth exposure information at an individual level, and even physiologic and target organ level as well. Yet, these approaches are extremely costly and labor intensive and, therefore, feasible only for application to small groups of subjects. These approaches will also need to clearly define the toxin of interest and determine whether personal or biologic monitoring would be possible over the longer periods. Further, it will also be necessary to discern whether non-target organ samples such as blood, urine, or hair would suffice to establish exposures affecting the brain. To date, there is little consensus on appropriate biomarkers for ambient air pollutants except possibly for some PAHs, mostly through measurement of DNA , protein, or albumin-adducts, although measurement of hydroxylated PAH metabolites in urine is another option (Castano-Vinyals et al. , 2004, Smith et al. , 2002). Other issues that need to be considered carefully regarding use of biomarkers is the ability to discern source contributions (e.g., dietary versus inhalation sources of PAHs) and appropriate timing of measurements. For example, urinary PAH metabolites measured at a single point in time will reflect exposures that occurred in the previous few days while DNA-adducts will reflect approximately a one month period (Barr et al. , 2005).

2. RESEARCH GAPS AND PRIORITY GOALS

A growing list of studies implicates air pollution as a significant CNS health concern. As described above, these earlier reports have identified the problem and are beginning to define the extent and mechanisms of these CNS effects. However, these initial findings are as of yet incomplete and emphasize the importance of additional scientific inquiry. To

address this issue, the NIEHS panel identified four critical research foci to move this developing field forward and address this emerging health concern, which are described in detail below.

2.1 Identifying the Neurotoxic Components of Air Pollution

The following topics were identified as critical areas of research:

1. Conduct toxicokinetics studies to examine: i) how the entry portal affects transport of pollutants to the brain, ii) the biotransformation, distribution, and elimination of pollutants from the brain, and iii) the influence of particle size and composition on transport and elimination from the brian.
2. Assess whether specific chemical (e.g. metals, PAHs, VOCs) and/or physical properties of PM (e.g., size: UF, $PM_{2.5}$ and PM_{10}) are responsible for the inflammatory/neurotoxic effects in the brain and CNS.
3. Identify populations (aged, young, genotype, low socioeconomic status, high stress, and ongoing CNS disease) that are vulnerable to air pollution in animal and epidemiology studies.

2.2 Revealing the Cellular and Molecular Mechanisms Driving Neuropathology

The following research priorities were identified as urgent priorities in the field:

1. Investigate the role of peripheral inflammatory and neurohormonal mediators (from respiratory tract and/or blood) on air pollution effects (neuroinflammation, CNS pathology, particle biokinetics, and behavior).
2. Explore the role of peripheral immune cells in air pollution-induced CNS effects.
3. Identify how CNS cell types (astrocyte, microglia, oligodendrocyte, and neurons) are affected by air pollution and their role in pathology.
4. Discern the effect of air pollution on BBB function and the consequent impact on CNS health.
5. Determine how the air pollution-induced effects on the CNS and cardiovascular diseases interact.

2.3 Human Research and Epidemiology

Specific human research priorities are to:

1. Explore the effect of specific air pollution components on increased risk for neurodevelopmental disorders (e.g. autism), neurodegenerative disease (e.g. AD and PD), and mental disorders (e.g. depression) in humans.
2. Evaluate whether observed CNS effects occur downstream or independent of cardiovascular effects or cerebrovascular damage. It will be particularly useful to examine air pollutant effects in adult cohorts that are well-characterized with respect to subclinical and clinical cardiovascular and cerebrovascular disease endpoints prior to or concurrently with the assessment of brain health.
3. Utilize refined exposure estimates to examine long-term air pollution effects on the brain over the life course. Although it likely is not feasible to follow subjects to ascertain lifetime exposures and associated health effects, adding an air pollution exposure assessment component to existing, ongoing populations with available information on residential history or extending the scope of outcome assessment in specific longitudinal air pollution cohort studies, which have developed

sophisticated spatio-temporal models for various air pollutants, would allow for the examination of CNS effects in various age groups in a relatively resource-efficient manner. Elucidating relevant windows of exposure could provide insight into mechanisms based on existing knowledge of neurodevelopmental and aging processes.

4. Investigate the CNS effects of acute air pollutant exposure, such as during reported peak ozone or particulate matter periods, using multiple time points in an effort to define temporal resolution, if and when it occurs.

5. Examine air pollution effects on the brain in sensitive subgroups, including genetically-susceptible populations, to highlight mechanisms of importance.

6. Evaluate subclinical outcomes of importance in CNS effects. Determining neurological and neurobehavioral outcomes examined in animal studies that translate to and can be investigated in human studies has the potential to be particularly informative. Also, taking advantage of MRI and other neuroimaging technologies can provide information regarding mechanisms. For example, the detection and location of subclinical white matter disease or infarcts could illuminate underlying disease processes at work.

2.4 Experimental Approach

The following recommendations for methodology and approach for future research were identified:

1. Adequate exposure assessment was revealed as a cross-cutting research goal across all discussion groups in the Workshop. Given that air pollution is a complex mixture and different exposures may have unique components contributing to CNS health, appropriate exposure characterization is mandatory for *in vitro*, *in vivo*, and epidemiological studies. A focus of such research should also include the identification of the separate roles of particulate versus soluble components in mediating response when the technology becomes available.

2. Numerous past studies have adopted the reductionist approach of combining several pollutants to make up a single atmosphere. While this has some utility, as does the single pollutant model for the purposes of mechanistic studies, it is likely to miss significant biological responses due to interactions that play a role in the overall health outcome. Thus, the use of real-world mixtures and ambient concentrations of these mixtures, including pollutants derived from both existing and new fuel technologies (e.g. biofuels and catalysts) would significantly advance our understanding of the vulnerability of the CNS to air pollutants.

3. There is a need to better characterize gene-environment (air pollution) interactions. Epigenetic factors may influence how air pollution can induce adverse effects on the brain and/or lung. Epigenetic factors may also account for the enhanced susceptibility of certain subpopulations including alterations in gene function during development or senescence. CNS health outcomes, such as cognitive performance and dementia ascertainment, should be incorporated into existing human/epidemiology exposure assessment campaigns.

4. There is a clear need to support near-lifetime exposure studies in rodents.

5. In addition to the measurements of mediators and pathological changes, behavioral endpoints will also be an important area of interest in human and animal studies.

3. CONCLUSION

Evidence is accumulating for air pollution related CNS effects at multiple levels, including modulation of molecular/neuochemical/pathobiological pathways, neuroinflammation, neurotoxicity, and neurobehavioral changes that implicate subclinical/clinical manifestation of disease. However, the extent of these effects contributing to ill health, the components of air pollution responsible and the molecular mechanisms underlying the phenomena are poorly understood. As such, there is significant need for thorough epidemiology, mechanistic, and translational studies to identify how air pollution affects CNS health with the goal of eventual identification of early markers of neuropathology, intervention, and prevention of disease. Identification of critical periods, vulnerable populations, and the use of environmentally relevant, life-time exposures will be key to understanding this human health concern. This research program will by necessity involve close collaborations amongst scientists from different fields, including atmospheric science, epidemiology (air pollution, developmental, and neuroepidemiology), clinical medicine (neurodevelopment, neurology, and psychiatry), inhalation and behavioral neurotoxicology, social sciences (including neuropsychology) and basic neuroscience.

Acknowledgments

This work was supported by NIEHS/NIH-DERT.

Abbreviations

PM	particulate matter
CNS	central nervous system
AD	Alzheimer’s disease
PD	Parkinson’s disease
BBB	blood brain barrier
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
PAHs	Polycyclic Aromatic Hydrocarbons
UF	ultrafine
TNF	tumor necrosis factor
TLR	toll-like receptor
CO	carbon monoxide
VOCs	volatile organic compounds
CYP	cytochrome P450

REFERENCES

Abbott NJ, Patabendige AA, Dolman DE, Yusof SR, Begley DJ. Structure and function of the blood-brain barrier. Neurobiol Dis. 2010; 37:13–25. [PubMed: 19664713]

Adar SD, Klein R, Klein BE, Szpiro AA, Cotch MF, Wong TY, et al. Air Pollution and the microvasculature: a cross-sectional assessment of in vivo retinal images in the population-based multi-ethnic study of atherosclerosis (MESA). PLoS Med. 2010; 7:e1000372. [PubMed: 21152417]

Amin-Zaki L, Elhassani S, Majeed MA, Clarkson TW, Doherty RA, Greenwood M. Intra-uterine Methylmercury Poisoning in Iraq. Pediatrics. 1974; 54:587–95. [PubMed: 4480317]

Antonini JM, Sriram K, Benkovic SA, Roberts JR, Stone S, Chen BT, et al. Mild steel welding fume causes manganese accumulation and subtle neuroinflammatory changes but not overt neuronal damage in discrete brain regions of rats after short-term inhalation exposure. Neurotoxicology. 2009; 30:915–25. [PubMed: 19782702]

Auchincloss AH, Diez Roux AV, Dvonch JT, Brown PL, Barr RG, Daviglus ML, et al. Associations between recent exposure to ambient fine particulate matter and blood pressure in the Multi-ethnic Study of Atherosclerosis (MESA). Environ Health Perspect. 2008; 116:486–91. [PubMed: 18414631]

Auerbach A, Hernandez ML. The effect of environmental oxidative stress on airway inflammation. Curr Opin Allergy Clin Immunol. 2012

Baccarelli A, Wright RO, Bollati V, Tarantini L, Litonjua AA, Suh HH, et al. Rapid DNA methylation changes after exposure to traffic particles. Am J Respir Crit Care Med. 2009; 179:572–8. [PubMed: 19136372]

Barr DB, Wang RY, Needham LL. Biologic monitoring of exposure to environmental chemicals throughout the life stages: requirements and issues for consideration for the National Children's Study. Environ Health Perspect. 2005; 113:1083–91. [PubMed: 16079083]

Bellinger D, Leviton A, Waternaux C, Neddleman N, Rabinowitz M. Longitudinal analyses of pre-and postnatal lead exposure and early cognitive development. N Engl J Med. 1987; 316:1037–43. [PubMed: 3561456]

Benson, P. CALINE4: A dispersion model for predicting air pollutant concentrations near roadways. California Department of Transportation; Sacramento, CA: 1989.

Block ML, Calderon-Garciduenas L. Air pollution: mechanisms of neuroinflammation and CNS disease. Trends Neurosci. 2009; 32:506–16. [PubMed: 19716187]

Block ML, Hong JS. Microglia and inflammation-mediated neurodegeneration: multiple triggers with a common mechanism. Prog Neurobiol. 2005; 76:77–98. [PubMed: 16081203]

Block ML, Hong JS. Chronic microglial activation and progressive dopaminergic neurotoxicity. Biochem Soc Trans. 2007; 35:1127–32. [PubMed: 17956294]

Block ML, Wu X, Pei Z, Li G, Wang T, Qin L, et al. Nanometer size diesel exhaust particles are selectively toxic to dopaminergic neurons: the role of microglia, phagocytosis, and NADPH oxidase. FASEB J. 2004; 18:1618–20. [PubMed: 15319363]

Block ML, Zecca L, Hong JS. Microglia-mediated neurotoxicity: uncovering the molecular mechanisms. Nat Rev Neurosci. 2007; 8:57–69. [PubMed: 17180163]

Bond JA, Harkema JR, Russell VI. Regional distribution of xenobiotic metabolizing enzymes in respiratory airways of dogs. Drug Metab Dispos. 1988; 16:116–24. [PubMed: 2894939]

Breysse PN, Diette GB, Matsui EC, Butz AM, Hansel NN, McCormack MC. Indoor air pollution and asthma in children. Proc Am Thorac Soc. 2010; 7:102–6. [PubMed: 20427579]

Brook RD, Rajagopalan S, Pope CA 3rd, Brook JR, Bhatnagar A, Diez-Roux AV, et al. Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the American Heart Association. Circulation. 2010; 121:2331–78. [PubMed: 20458016]

Budimir A. Metal ions, Alzheimer's disease and chelation therapy. Acta Pharm. 2011; 61:1–14. [PubMed: 21406339]

Busse PJ, Mathur SK. Age-related changes in immune function: Effect on airway inflammation. J Allergy Clin Immun. 2010; 126:690–9. [PubMed: 20920759]

Calderon-Garciduenas L, Azzarelli B, Acuna H, Garcia R, Gambling TM, Osnaya N, et al. Air pollution and brain damage. Toxicol Pathol. 2002; 30:373–89. [PubMed: 12051555]

Calderon-Garciduenas L, Franco-Lira M, Henriquez-Roldan C, Osnaya N, Gonzalez-Maciel A, Reynoso-Robles R, et al. Urban air pollution: influences on olfactory function and pathology in exposed children and young adults. Exp Toxicol Pathol. 2010; 62:91–102. [PubMed: 19297138]

Calderon-Garciduenas L, Kavanaugh M, Block M, D'Angiulli A, Delgado-Chavez R, Torres-Jardon R, et al. Neuroinflammation, hyperphosphorylated tau, diffuse amyloid plaques, and down-regulation of the cellular prion protein in air pollution exposed children and young adults. J Alzheimers Dis. 2012; 28:93–107. [PubMed: 21955814]

Calderon-Garciduenas L, Mora-Tiscareno A, Ontiveros E, Gomez-Garza G, Barragan-Mejia G, Broadway J, et al. Air pollution, cognitive deficits and brain abnormalities: a pilot study with children and dogs. Brain Cogn. 2008a; 68:117–27. [PubMed: 18550243]

Calderon-Garciduenas L, Reed W, Maronpot RR, Henriquez-Roldan C, Delgado-Chavez R, Calderon-Garciduenas A, et al. Brain inflammation and Alzheimer's-like pathology in individuals exposed to severe air pollution. Toxicol Pathol. 2004; 32:650–8. [PubMed: 15513908]

Calderon-Garciduenas L, Solt AC, Henriquez-Roldan C, Torres-Jardon R, Nuse B, Herritt L, et al. Long-term air pollution exposure is associated with neuroinflammation, an altered innate immune response, disruption of the blood-brain barrier, ultrafine particulate deposition, and accumulation of amyloid beta-42 and alpha-synuclein in children and young adults. Toxicol Pathol. 2008b; 36:289–310. [PubMed: 18349428]

Campbell A, Araujo JA, Li H, Sioutas C, Kleinman M. Particulate matter induced enhancement of inflammatory markers in the brains of apolipoprotein E knockout mice. J Nanosci Nanotechnol. 2009; 9:5099–104. [PubMed: 19928188]

Campbell A, Oldham M, Becaria A, Bondy SC, Meacher D, Sioutas C, et al. Particulate matter in polluted air may increase biomarkers of inflammation in mouse brain. Neurotoxicology. 2005; 26:133–40. [PubMed: 15527881]

Carrillo-Esper R. [Innate immunity, Toll receptor and sepsis]. Cir Cir. 2003; 71:252–8. [PubMed: 14617415]

Carvey PM, Punati A, Newman MB. Progressive dopamine neuron loss in Parkinson's disease: the multiple hit hypothesis. Cell Transplant. 2006; 15:239–50. [PubMed: 16719059]

Castano-Vinyals G, D'Errico A, Malats N, Kogevinas M. Biomarkers of exposure to polycyclic aromatic hydrocarbons from environmental air pollution. Occup Environ Med. 2004; 61:e12. [PubMed: 15031403]

Castro-Giner F, Kunzli N, Jacquemin B, Forsberg B, de Cid R, Sunyer J, et al. Traffic-related air pollution, oxidative stress genes, and asthma (ECHRS). Environmental Health Perspectives. 2009; 117:1919–24. [PubMed: 20049212]

Chahine LM, Stern MB. Diagnostic markers for Parkinson's disease. Curr Opin Neurol. 2011

Chen JC, Schwartz J. Neurobehavioral effects of ambient air pollution on cognitive performance in US adults. Neurotoxicology. 2009; 30:231–9. [PubMed: 19150462]

Chen L, Yokel RA, Hennig B, Toborek M. Manufactured aluminum oxide nanoparticles decrease expression of tight junction proteins in brain vasculature. J Neuroimmune Pharmacol. 2008; 3:286–95. [PubMed: 18830698]

Clougherty J, Levy JI, Kubzansky LD, Ryan B, Franco Suglia S, Jacobson Canner M, et al. The effects of traffic-related air pollution and exposure to violence on urban asthma etiology. Environ Health Perspect. 2007; 115:1140–6. [PubMed: 17687439]

Cretu DI, Sovrea A, Ignat RM, Filip A, Bidian C, Cretu A. Morpho-pathological and physiological changes of the brain and liver after ozone exposure. Rom J Morphol Embryol. 2010; 51:701–6. [PubMed: 21103629]

Croes BE, Fujita EM. Overview of the 1997 Southern California Ozone Study (SCOS97-NARSTO). Atmos Environ. 2003; 37:S3–S26.

Cruts B, van Etten L, Tornqvist H, Blomberg A, Sandstrom T, Mills NL, et al. Exposure to diesel exhaust induces changes in EEG in human volunteers. Part Fibre Toxicol. 2008; 5:4. [PubMed: 18334019]

Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci. 2008; 9:46–56. [PubMed: 18073775]

Derijk RH. Single nucleotide polymorphisms related to HPA axis reactivity. Neuroimmunomodulation. 2009; 16:340–52. [PubMed: 19571595]

Derijk RH, Schaaf M, de Kloet ER. Glucocorticoid receptor variants: clinical implications. J Steroid Biochem Mol Biol. 2002; 81:103–22. [PubMed: 12137800]

Diez Roux AV, Auchincloss AH, Franklin TG, Raghunathan T, Barr RG, Kaufman J, et al. Long-term exposure to ambient particulate matter and prevalence of subclinical atherosclerosis in the Multi-Ethnic Study of Atherosclerosis. Am J Epidemiol. 2008; 167:667–75. [PubMed: 18227099]

Donnan GA, McNeil JJ, Adena MA, Doyle AE, O'Malley HM, Neill GC. Smoking as a risk factor for cerebral ischaemia. Lancet. 1989; 2:643–7. [PubMed: 2570900]

Dorman DC, Brenneman KA, McElveen AM, Lynch SE, Roberts KC, Wong BA. Olfactory transport: a direct route of delivery of inhaled manganese phosphate to the rat brain. J Toxicol Environ Health A. 2002; 65:1493–511. [PubMed: 12396865]

Drake KA, Galanter JM, Burchard EG. Race, ethnicity and social class and the complex etiologies of asthma. Pharmacogenomics. 2008; 9:453–62. [PubMed: 18384258]

Edwards SC, Jedrychowski W, Butscher M, Camann D, Kieltyka A, Mroz E, et al. Prenatal exposure to airborne polycyclic aromatic hydrocarbons and children's intelligence at 5 years of age in a prospective cohort study in Poland. Environ Health Perspect. 2010; 118:1326–31. [PubMed: 20406721]

Eisner MD, Anthonisen N, Coultas D, Kuenzli N, Perez-Padilla R, Postma D, et al. An official American Thoracic Society public policy statement: Novel risk factors and the global burden of chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2010; 182:693–718. [PubMed: 20802169]

Elder A, Gelein R, Silva V, Feikert T, Opanashuk L, Carter J, et al. Translocation of inhaled ultrafine manganese oxide particles to the central nervous system. Environ Health Perspect. 2006; 114:1172–8. [PubMed: 16882521]

Engel SM, Berkowitz GS, Barr DB, Teitelbaum SL, Siskind J, Meisel SJ, et al. Prenatal organophosphate metabolite and organochlorine levels and performance on the Brazelton Neonatal Behavioral Assessment Scale in a multiethnic pregnancy cohort. Am J Epidemiol. 2007; 165:1397–404. [PubMed: 17406008]

Faustman EM, Silbernagel SM, Fenske RA, Burbacher TM, Ponce RA. Mechanisms underlying Children's susceptibility to environmental toxicants. Environ Health Perspect. 2000; 108(Suppl 1): 13–21. [PubMed: 10698720]

Feron VJ, Arts JH, Kuper CF, Slootweg PJ, Woutersen RA. Health risks associated with inhaled nasal toxicants. Crit Rev Toxicol. 2001; 31:313–47. [PubMed: 11405443]

Finkelstein MM, Jerrett M. A study of the relationships between Parkinson's disease and markers of traffic-derived and environmental manganese air pollution in two Canadian cities. Environ Res. 2007; 104:420–32. [PubMed: 17445792]

Finnerty K, Choi JE, Lau A, Davis-Gorman G, Diven C, Seaver N, et al. Instillation of coarse ash particulate matter and lipopolysaccharide produces a systemic inflammatory response in mice. J Toxicol Environ Health A. 2007; 70:1957–66. [PubMed: 17966067]

Fitz, DR.; Bufalino, C. Measurement of PM10 emission factors from paved roads using on-board particle sensors. US Environmental Protection Agency 11th Annual Emission Inventory Conference, Emission Inventories - Partnering for the Future; Atlanta, Georgia. 2002;

Fonken LK, Xu X, Weil ZM, Chen G, Sun Q, Rajagopalan S, et al. Air pollution impairs cognition, provokes depressive-like behaviors and alters hippocampal cytokine expression and morphology. Mol Psychiatry. 2011; 16:987–95. 73. [PubMed: 21727897]

Freire C, Ramos R, Puertas R, Lopez-Espinosa MJ, Julvez J, Aguilera I, et al. Association of traffic-related air pollution with cognitive development in children. J Epidemiol Community Health. 2010; 64:223–8. [PubMed: 19679705]

Geiser M, Rothen-Rutishauser B, Kapp N, Schurch S, Kreyling W, Schulz H, et al. Ultrafine particles cross cellular membranes by nonphagocytic mechanisms in lungs and in cultured cells. Environ Health Perspect. 2005; 113:1555–60. [PubMed: 16263511]

Genter MB, Deamer NJ, Blake BL, Wesley DS, Levi PE. Olfactory toxicity of methimazole: dose-response and structure-activity studies and characterization of flavin-containing monooxygenase activity in the Long-Evans rat olfactory mucosa. Toxicol Pathol. 1995; 23:477–86. [PubMed: 7501959]

Genter MB, Kendig EL, Knutson MD. Uptake of materials from the nasal cavity into the blood and brain: are we finally beginning to understand these processes at the molecular level? Ann N Y Acad Sci. 2009; 1170:623–8. [PubMed: 19686203]

Gerlofs-Nijland ME, van Berlo D, Cassee FR, Schins RP, Wang K, Campbell A. Effect of prolonged exposure to diesel engine exhaust on proinflammatory markers in different regions of the rat brain. Part Fibre Toxicol. 2010; 7:12. [PubMed: 20478040]

Ghersi-Egea JF, Minn A, Siest G. A new aspect of the protective functions of the blood-brain barrier: activities of four drug-metabolizing enzymes in isolated rat brain microvessels. Life Sci. 1988; 42:2515–23. [PubMed: 3131610]

Gill EA, Curl CL, Adar SD, Allen RW, Auchincloss AH, O'Neill MS, et al. Air pollution and cardiovascular disease in the Multi-Ethnic Study of Atherosclerosis. Prog Cardiovasc Dis. 2011; 53:353–60. [PubMed: 21414470]

Guxens M, Sunyer J. A review of epidemiological studies on neuropsychological effects of air pollution. Swiss Med Wkly. 2012; 141:w13322. [PubMed: 22252905]

Hahn YK, Vo P, Fitting S, Block ML, Hauser KF, Knapp PE. beta-Chemokine production by neural and glial progenitor cells is enhanced by HIV-1 Tat: effects on microglial migration. J Neurochem. 2010; 114:97–109. [PubMed: 20403075]

Hartz AM, Bauer B, Block ML, Hong JS, Miller DS. Diesel exhaust particles induce oxidative stress, proinflammatory signaling, and P-glycoprotein up-regulation at the blood-brain barrier. FASEB J. 2008; 22:2723–33. [PubMed: 18474546]

Hawkes CH, Del Tredici K, Braak H. Parkinson's disease: a dual-hit hypothesis. Neuropathology and applied neurobiology. 2007; 33:599–614. [PubMed: 17961138]

Henrotin JB, Besancenot JP, Bejot Y, Giroud M. Short-term effects of ozone air pollution on ischaemic stroke occurrence: a case-crossover analysis from a 10-year population-based study in Dijon, France. Occup Environ Med. 2007; 64:439–45. [PubMed: 17409181]

Hetland RB, Cassee FR, Lag M, Refsnes M, Dybing E, Schwarze PE. Cytokine release from alveolar macrophages exposed to ambient particulate matter: heterogeneity in relation to size, city and season. Part Fibre Toxicol. 2005; 2:4. [PubMed: 16105184]

Hozumi I, Hasegawa T, Honda A, Ozawa K, Hayashi Y, Hashimoto K, et al. Patterns of levels of biological metals in CSF differ among neurodegenerative diseases. J Neurol Sci. 2011; 303:95–9. [PubMed: 21292280]

Hunter DD, Dey RD. Identification and neuropeptide content of trigeminal neurons innervating the rat nasal epithelium. Neuroscience. 1998; 83:591–9. [PubMed: 9460765]

Hunter DD, Undem BJ. Identification and substance P content of vagal afferent neurons innervating the epithelium of the guinea pig trachea. Am J Resp Crit Care. 1999; 159:1943–8.

Jang HM, Boltz D, Sturm-Ramirez K, Shepherd KR, Jiao Y, Webster R, et al. Highly pathogenic H5N1 influenza virus can enter the central nervous system and induce neuroinflammation and neurodegeneration. P Natl Acad Sci USA. 2009; 106:14063–8.

Kaufman JD. Does air pollution accelerate progression of atherosclerosis? J Am Coll Cardiol. 2010; 56:1809–11. [PubMed: 21087708]

Laviola G, Hannan AJ, Macri S, Solinas M, Jaber M. Effects of enriched environment on animal models of neurodegenerative diseases and psychiatric disorders. Neurobiol Dis. 2008; 31:159–68. [PubMed: 18585920]

Leavens TL, Rao D, Andersen ME, Dorman DC. Evaluating transport of manganese from olfactory mucosa to striatum by pharmacokinetic modeling. Toxicol Sci. 2007; 97:265–78. [PubMed: 17372280]

Lehnardt S. Innate immunity and neuroinflammation in the CNS: the role of microglia in Toll-like receptor-mediated neuronal injury. Glia. 2010; 58:253–63. [PubMed: 19705460]

Levenson JM, Roth TL, Lubin FD, Miller CA, Huang IC, Desai P, et al. Evidence that DNA (cytosine-5) methyltransferase regulates synaptic plasticity in the hippocampus. Journal of Biological Chemistry. 2006; 281:15763–73. [PubMed: 16606618]

Levesque S, Surace MJ, McDonald J, Block ML. Air pollution & the brain: Subchronic diesel exhaust exposure causes neuroinflammation and elevates early markers of neurodegenerative disease. J Neuroinflammation. 2011a; 8:105. [PubMed: 21864400]

Levesque S, Taetzsch T, Lull ME, Kodavanti U, Stadler K, Wagner A, et al. Diesel exhaust activates and primes microglia: air pollution, neuroinflammation, and regulation of dopaminergic neurotoxicity. Environ Health Perspect. 2011b; 119:1149–55. [PubMed: 21561831]

Lewis J, Bench G, Myers O, Tinner B, Staines W, Barr E, et al. Trigeminal uptake and clearance of inhaled manganese chloride in rats and mice. Neurotoxicology. 2005; 26:113–23. [PubMed: 15527879]

Liao D, Duan Y, Whitsel EA, Zheng ZJ, Heiss G, Chinchilli VM, et al. Association of higher levels of ambient criteria pollutants with impaired cardiac autonomic control: a population-based study. Am J Epidemiol. 2004; 159:768–77. [PubMed: 15051586]

Livertoux MH, Lagrange P, Minn A. The superoxide production mediated by the redox cycling of xenobiotics in rat brain microsomes is dependent on their reduction potential. Brain Res. 1996; 725:207–16. [PubMed: 8836527]

Lockman PR, Koziara JM, Mumper RJ, Allen DD. Nanoparticle surface charges alter blood-brain barrier integrity and permeability. J Drug Target. 2004; 12:635–41. [PubMed: 15621689]

Longo V, Ingelman-Sundberg M, Amato G, Salvetti A, Gervasi PG. Effect of starvation and chlormethiazole on cytochrome P450s of rat nasal mucosa. Biochem Pharmacol. 2000; 59:1425–32. [PubMed: 10751552]

Lopez IA, Acuna D, Beltran-Parrazal L, Espinosa-Jeffrey A, Edmond J. Oxidative stress and the deleterious consequences to the rat cochlea after prenatal chronic mild exposure to carbon monoxide in air. Neuroscience. 2008; 151:854–67. [PubMed: 18155845]

Lucchini RG, Dorman DC, Elder A, Veronesi B. Neurological impacts from inhalation of pollutants and the nose-brain connection. Neurotoxicology. 2011

Lucchini RG, Martin CJ, Doney BC. From manganism to manganese-induced parkinsonism: a conceptual model based on the evolution of exposure. Neuromolecular Med. 2009; 11:311–21. [PubMed: 20012385]

Lull ME, Block ML. Microglial activation and chronic neurodegeneration. Neurotherapeutics. 2010; 7:354–65. [PubMed: 20880500]

Marsh DO, Myers GJ, Clarkson TW, Amin-Zaki l, Tikriti S, Majeed MA. Fetal methylmercury poisoning: Clinical and toxicological data on 29 cases. Annals of Neurology. 1980; 7:348–53. [PubMed: 7377761]

Mateen FJ, Brook RD. Air pollution as an emerging global risk factor for stroke. JAMA. 2011; 305:1240–1. [PubMed: 21427378]

McGeer EG, McGeer PL. Neuroinflammation in Alzheimer's disease and mild cognitive impairment: a field in its infancy. J Alzheimers Dis. 2010; 19:355–61. [PubMed: 20061650]

McGeer PL, Itagaki S, Boyes BE, McGeer EG. Reactive microglia are positive for HLA-DR in the substantia nigra of Parkinson's and Alzheimer's disease brains. Neurology. 1988; 38:1285–91. [PubMed: 3399080]

Mekhail M, Almazan G, Tabrizian M. Oligodendrocyte-protection and remyelination post-spinal cord injuries: A review. Prog Neurobiol. 2012; 96:322–39. [PubMed: 22307058]

Meloni G, Vasak M. Redox activity of alpha-synuclein-Cu is silenced by Zn-metallothionein-3. Free Radic Biol Med. 2011; 50:1471–9. [PubMed: 21320589]

Mendola P, Selevan SG, Gutter S, Rice D. Environmental factors associated with a spectrum of neurodevelopmental deficits. Ment Retard Dev Disabil Res Rev. 2002; 8:188–97. [PubMed: 12216063]

Meyer U, Feldon J, Fatemi SH. In-vivo rodent models for the experimental investigation of prenatal immune activation effects in neurodevelopmental brain disorders. Neuroscience and biobehavioral reviews. 2009; 33:1061–79. [PubMed: 19442688]

Miller DS. Regulation of P-glycoprotein and other ABC drug transporters at the blood-brain barrier. Trends Pharmacol Sci. 2010; 31:246–54. [PubMed: 20417575]

Min JY, Paek D, Cho SI, Min KB. Exposure to environmental carbon monoxide may have a greater negative effect on cardiac autonomic function in people with metabolic syndrome. Science Total Environment. 2009; 61:49–56.

Minn A, Leclerc S, Heydel JM, Minn AL, Denizcot C, Cattarelli M, et al. Drug transport into the mammalian brain: the nasal pathway and its specific metabolic barrier. J Drug Target. 2002; 10:285–96. [PubMed: 12164377]

Morales E, Julvez J, Torrent M, de Cid R, Guxens M, Bustamante M, et al. Association of early-life exposure to household gas appliances and indoor nitrogen dioxide with cognition and attention behavior in preschoolers. Am J Epidemiol. 2009; 169:1327–36. [PubMed: 19395695]

Morgan JT, Chana G, Pardo CA, Achim C, Semendeferi K, Buckwalter J, et al. Microglial activation and increased microglial density observed in the dorsolateral prefrontal cortex in autism. Biol Psychiatry. 2010; 68:368–76. [PubMed: 20674603]

Morgan TE, Davis DA, Iwata N, Tanner JA, Snyder D, Ning Z, et al. Glutamatergic neurons in rodent models respond to nanoscale particulate urban air pollutants in vivo and in vitro. Environ Health Perspect. 2011; 119:1003–9. [PubMed: 21724521]

Mutlu EA, Engen PA, Soberanes S, Urich D, Forsyth CB, Nigdelioglu R, et al. Particulate matter air pollution causes oxidant-mediated increase in gut permeability in mice. Part Fibre Toxicol. 2011; 8:19. [PubMed: 21658250]

Namdeo A, Tiwary A, Farrow E. Estimation of age-related vulnerability to air pollution: Assessment of respiratory health at local scale. Environ Int. 2011; 37:829–37. [PubMed: 21420174]

Nel A. Atmosphere. Air pollution-related illness: effects of particles. Science. 2005; 308:804–6. [PubMed: 15879201]

O'Brien JT. Vascular cognitive impairment. Am J Geriatr Psychiatry. 2006; 14:724–33. [PubMed: 16943169]

O'Neill MS, Jerrett M, Kawachi I, Levy JI, Cohen AJ, Gouveia N, et al. Health, wealth, and air pollution: advancing theory and methods. Environ Health Perspect. 2003; 111:1861–70. [PubMed: 14644658]

O'Neill MS, Kinney PL, Cohen AJ. Environmental equity in air quality management: local and international implications for human health and climate change. J Toxicol Environ Health A. 2008; 71:570–7. [PubMed: 18569628]

Oberdorster G, Elder A, Rinderknecht A. Nanoparticles and the brain: cause for concern? J Nanosci Nanotechnol. 2009; 9:4996–5007. [PubMed: 19928180]

Oberdorster G, Sharp Z, Atudorei V, Elder A, Gelein R, Kreyling W, et al. Translocation of inhaled ultrafine particles to the brain. Inhal Toxicol. 2004; 16:437–45. [PubMed: 15204759]

Oberdorster G, Utell MJ. Ultrafine particles in the urban air: to the respiratory tract--and beyond? Environ Health Perspect. 2002; 110:A440–1. [PubMed: 12153769]

Park SK, Auchincloss AH, O'Neill MS, Prineas R, Correa JC, Keeler J, et al. Particulate air pollution, metabolic syndrome, and heart rate variability: the multi-ethnic study of atherosclerosis (MESA). Environ Health Perspect. 2010; 118:1406–11. [PubMed: 20529761]

Park SK, O'Neill MS, Vokonas PS, Sparrow D, Schwartz J. Effects of air pollution on heart rate variability: the VA normative aging study. Environ Health Perspect. 2005; 113:304–9. [PubMed: 15743719]

Patel MM, Quinn JW, Jung KH, Hoepner L, Diaz D, Perzanowski M, et al. Traffic density and stationary sources of air pollution associated with wheeze, asthma, and immunoglobulin E from birth to age 5 years among New York City children. Environ Res. 2011; 111:1222–9. [PubMed: 21855059]

Pearce EN, Braverman LE. Environmental pollutants and the thyroid. Best Pract Res Clin Endocrinol Metab. 2009; 23:801–13. [PubMed: 19942155]

Pereyra-Munoz N, Rugerio-Vargas C, Angoa-Perez M, Borgonio-Perez G, Rivas-Arancibia S. Oxidative damage in substantia nigra and striatum of rats chronically exposed to ozone. J Chem Neuroanat. 2006; 31:114–23. [PubMed: 16236481]

Perrin RJ, Craig-Schapiro R, Malone JP, Shah AR, Gilmore P, Davis AE, et al. Identification and validation of novel cerebrospinal fluid biomarkers for staging early Alzheimer's disease. PLoS One. 2011; 6:e16032. [PubMed: 21264269]

Perry VH. The influence of systemic inflammation on inflammation in the brain: implications for chronic neurodegenerative disease. Brain, behavior, and immunity. 2004; 18:407–13.

Perry VH, Cunningham C, Holmes C. Systemic infections and inflammation affect chronic neurodegeneration. Nat Rev Immunol. 2007; 7:161–7. [PubMed: 17220915]

Peters A, Frohlich M, Doring A, Immervoll T, Wichmann HE, Hutchinson WL, et al. Particulate air pollution is associated with an acute phase response in men; results from the MONICA-Augsburg Study. Eur Heart J. 2001; 22:1198–204. [PubMed: 11440492]

Peters A, Veronesi B, Calderon-Garciduenas L, Gehr P, Chen LC, Geiser M, et al. Translocation and potential neurological effects of fine and ultrafine particles a critical update. Part Fibre Toxicol. 2006; 3:13. [PubMed: 16961926]

Peters JL, Weisskopf MG, Spiro Ar, Schwartz J, Sparrow D, Nie H, et al. Interaction of stress, lead burden, and age on cognition in older men: the VA Normative Aging Study. Environmental Health Perspectives. 2010; 118:505–10. [PubMed: 20064786]

Petronis A. Epigenetics and bipolar disorder: new opportunities and challenges. Am J Med Genet C Semin Med Genet. 2003; 123C:65–75. [PubMed: 14601038]

Phalen RF, Mendez LB, Oldham MJ. New developments in aerosol dosimetry. Inhal Toxicol. 2010; 22(Suppl 2):6–14. [PubMed: 20939685]

Pope CA. Epidemiology of fine particulate air pollution and human health: Biologic mechanisms and who's at risk? Environ Health Persp. 2000; 108:713–23.

Pope CA 3rd, Burnett RT, Thun MJ, Calle EE, Krewski D, Ito K, et al. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. JAMA. 2002; 287:1132–41. [PubMed: 11879110]

Power MC, Weisskopf MG, Alexeeff SE, Coull BA, Spiro A 3rd, Schwartz J. Traffic-related air pollution and cognitive function in a cohort of older men. Environ Health Perspect. 2011; 119:682–7. [PubMed: 21172758]

Qin L, Wu X, Block ML, Liu Y, Breese GR, Hong JS, et al. Systemic LPS causes chronic neuroinflammation and progressive neurodegeneration. Glia. 2007; 55:453–62. [PubMed: 17203472]

Racette BA, McGee-Minnich L, Moerlein SM, Mink JW, Videen TO. Perlmutter JS. Welding-related parkinsonism: clinical features, treatment, and pathophysiology. Neurology. 2001; 56:8–13.

Ranft U, Schikowski T, Sugiri D, Krutmann J, Kramer U. Long-term exposure to traffic-related particulate matter impairs cognitive function in the elderly. Environ Res. 2009; 109:1004–11. [PubMed: 19733348]

Rao DB, Wong BA, McManus BE, McElveen AM, James AR, Dorman DC. Inhaled iron, unlike manganese, is not transported to the rat brain via the olfactory pathway. Toxicology and applied pharmacology. 2003; 193:116–26. [PubMed: 14613722]

Rivas-Arancibia S, Dorado-Martinez C, Colin-Barenque L, Kendrick KM, de la Riva C, Guevara-Guzman R. Effect of acute ozone exposure on locomotor behavior and striatal function. Pharmacol Biochem Behav. 2003; 74:891–900. [PubMed: 12667904]

Rivas-Arancibia S, Guevara-Guzman R, Lopez-Vidal Y, Rodriguez-Martinez E, Zanardo-Gomes M, Angoa-Perez M, et al. Oxidative stress caused by ozone exposure induces loss of brain repair in the hippocampus of adult rats. Toxicol Sci. 2010; 113:187–97. [PubMed: 19833740]

Rivest S, Lacroix S, Vallieres L, Nadeau S, Zhang J, Laflamme N. How the blood talks to the brain parenchyma and the paraventricular nucleus of the hypothalamus during systemic inflammatory and infectious stimuli. Proc Soc Exp Biol Med. 2000; 223:22–38. [PubMed: 10632958]

Rodier PM. Environmental causes of central nervous system maldevelopment. Pediatrics. 2004; 113:1076–83. [PubMed: 15060202]

Sahsuvaroglu T, Arian A, Kanaroglou P, Finkelstein N, Newbold B, Jerrett M. A land use regression model for predicting ambient concentrations of nitrgen dioxide in Hamilton, Ontario, Canada. J Air and Waste Management Association. 2006; 56:1059–69.

Sama P, Long TC, Hester S, Tajuba J, Parker J, Chen LC, et al. The cellular and genomic response of an immortalized microglia cell line (BV2) to concentrated ambient particulate matter. Inhal Toxicol. 2007; 19:1079–87. [PubMed: 17957548]

Santiago-Lopez D, Bautista-Martinez JA, Reyes-Hernandez CI, Aguilar-Martinez M, Rivas-Arancibia S. Oxidative stress, progressive damage in the substantia nigra and plasma dopamine oxidation, in rats chronically exposed to ozone. Toxicol Lett. 2010; 197:193–200. [PubMed: 20541596]

Santucci D, Sorace A, Francia N, Aloe L, Alleva E. Prolonged prenatal exposure to low-level ozone affects aggressive behaviour as well as NGF and BDNF levels in the central nervous system of CD-1 mice. Behav Brain Res. 2006; 166:124–30. [PubMed: 16263182]

Schnaas L, Rothenberg SJ, Flores M, Martinez S, Hernandez C, Osorio E, et al. Reduced intellectual development in children with prenatal lead exposure. Environmental Health Perspectives. 2006; 114:791–7. [PubMed: 16675439]

Schneider JS, Lee MH, Anderson DW, Zuck L, Lidsky TI. Enriched environment during development is protective against lead-induced neurotoxicity. Brain Research. 2001; 896:48–55. [PubMed: 11277972]

Schwela D, Kephalopoulos S, Prasher D. Confounding or aggravating factors in noise-induced health effects: air pollutants and other stressors. Noise Health. 2005; 7:41–50. [PubMed: 16417704]

Seaton A, Soutar A, Crawford V, Elton R, McNerlan S, Cherrie J, et al. Particulate air pollution and the blood. Thorax. 1999; 54:1027–32. [PubMed: 10525563]

Shahbazian MD, Zoghbi HY. Rett syndrome and MeCP2: linking epigenetics and neuronal function. Am J Hum Genet. 2002; 71:1259–72. [PubMed: 12442230]

Shi M, Bradner J, Hancock AM, Chung KA, Quinn JF, Peskind ER, et al. Cerebrospinal fluid biomarkers for Parkinson disease diagnosis and progression. Ann Neurol. 2011; 69:570–80. [PubMed: 21400565]

Shoenfelt J, Mitkus RJ, Zeisler R, Spatz RO, Powell J, Fenton MJ, et al. Involvement of TLR2 and TLR4 in inflammatory immune responses induced by fine and coarse ambient air particulate matter. J Leukoc Biol. 2009; 86:303–12. [PubMed: 19406832]

Smith CJ, Huang W, Walcott CJ, Turner W, Grainger J, Patterson DG Jr. Quantification of monohydroxy-PAH metabolites in urine by solid-phase extraction with isotope dilution-GC-MS. Anal Bioanal Chem. 2002; 372:216–20. [PubMed: 11939197]

Sorace A, de Acetis L, Alleva E, Santucci D. Prolonged exposure to low doses of ozone: short- and long-term changes in behavioral performance in mice. Environ Res. 2001; 85:122–34. [PubMed: 11161662]

Soukup JM, Becker S. Human alveolar macrophage responses to air pollution particulates are associated with insoluble components of coarse material, including particulate endotoxin. Toxicol Appl Pharmacol. 2001; 171:20–6. [PubMed: 11181108]

Sparkman NL, Johnson RW. Neuroinflammation associated with aging sensitizes the brain to the effects of infection or stress. Neuroimmunomodulation. 2008; 15:323–30. [PubMed: 19047808]

Stampfer MJ. Cardiovascular disease and Alzheimer's disease: common links. J Intern Med. 2006; 260:211–23. [PubMed: 16918818]

Su JG, Jerrett M, Beckerman B, Wilhelm M, Ghosh JK, Ritz B. Predicting traffic-related air pollution in Los Angeles using a distance decay regression selection strategy. Environ Res. 2009; 109:657–70. [PubMed: 19540476]

Suglia SF, Gryparis A, Wright RO, Schwartz J, Wright RJ. Association of black carbon with cognition among children in a prospective birth cohort study. Am J Epidemiol. 2008; 167:280–6. [PubMed: 18006900]

Sunderman FW Jr. Nasal toxicity, carcinogenicity, and olfactory uptake of metals. Ann Clin Lab Sci. 2001a; 31:3–24. [PubMed: 11314863]

Sunderman FW Jr. Nasal toxicity, carcinogenicity, and olfactory uptake of metals. Annals of Clinical and Laboratory Science. 2001b; 31:3–24. [PubMed: 11314863]

Suzuki T, Oshio S, Iwata M, Saburi H, Odagiri T, Udagawa T, et al. In utero exposure to a low concentration of diesel exhaust affects spontaneous locomotor activity and monoaminergic system in male mice. Part Fibre Toxicol. 2010; 7:7. [PubMed: 20331848]

Thompson AM, Zanobetti A, Silverman F, Schwartz J, Coull B, Urch B, et al. Baseline repeated measures from controlled human exposure studies: associations between ambient air pollution exposure and the systemic inflammatory biomarkers IL-6 and fibrinogen. Environmental Health Perspectives. 2010; 118:120–4. [PubMed: 20056584]

Thomson EM, Kumarathasan P, Calderon-Garciduenas L, Vincent R. Air pollution alters brain and pituitary endothelin-1 and inducible nitric oxide synthase gene expression. Environmental Research. 2007; 105:224–33. [PubMed: 17662977]

Tilson HA, Jacobson JL, Rogan WJ. Polychlorinated biphenyls and the developing nervous system: Cross-species comparisons. Neurotoxicology and Teratology. 1990; 12:239–48. [PubMed: 2115098]

Tjalve H, Henriksson J. Uptake of metals in the brain via olfactory pathways. Neurotoxicology. 1999; 20:181–95. [PubMed: 10385882]

Tomei F, Rosati MV, Ciarrocca M, Baccolo TP, Gaballo M, Caciari T, et al. Plasma cortisol levels and workers exposed to urban pollutants. Ind Health. 2003; 41:320–6. [PubMed: 14620667]

Tonelli LH, Holmes A, Postolache TT. Intranasal immune challenge induces sex-dependent depressive-like behavior and cytokine expression in the brain. Neuropsychopharmacology. 2008; 33:1038–48. [PubMed: 17593929]

Tonelli LH, Postolache TT. Airborne inflammatory factors: “from the nose to the brain”. Front Biosci (Schol Ed). 2010; 2:135–52. [PubMed: 20036935]

Tsuang M, Stone W, Faraone S. Genes, environment and schizophrenia. Br J Psychiatry Suppl. 2001; 40:s18–24. [PubMed: 11315219]

Upadhyay UD, Holbrook EH. Olfactory loss as a result of toxic exposure. Otolaryngol Clin North Am. 2004; 37:1185–207. [PubMed: 15563910]

Van Hee VC, Adar SD, Szpiro AA, Barr RG, Bluemke DA, Diez Roux AV, et al. Exposure to traffic and left ventricular mass and function: the Multi-Ethnic Study of Atherosclerosis. Am J Respir Crit Care Med. 2009; 179:827–34. [PubMed: 19164703]

Van Hee VC, Adar SD, Szpiro AA, Barr RG, Roux AD, Bluemke DA, et al. Common genetic variation, residential proximity to traffic exposure, and left ventricular mass: the multi-ethnic study of atherosclerosis. Environ Health Perspect. 2010; 118:962–9. [PubMed: 20308035]

Veronesi B, Makwana O, Pooler M, Chen LC. Effects of subchronic exposures to concentrated ambient particles. VII. Degeneration of dopaminergic neurons in Apo E−/− mice. Inhal Toxicol. 2005; 17:235–41. [PubMed: 15804941]

Villeneuve PJ, Chen L, Stieb D, Rowe BH. Associations between outdoor air pollution and emergency department visits for stroke in Edmonton, Canada. Eur J Epidemiol. 2006; 21:689–700. [PubMed: 17048082]

Voigt JM, Guengerich FP, Baron J. Localization and induction of cytochrome P450 1A1 and aryl hydrocarbon hydroxylase activity in rat nasal mucosa. J Histochem Cytochem. 1993; 41:877–85. [PubMed: 8315279]

Volk HE, Hertz-Picciotto I, Delwiche L, Lurmann F, McConnell R. Residential proximity to freeways and autism in the CHARGE study. Environ Health Perspect. 2011; 119:873–7. [PubMed: 21156395]

von Bernhardi R, Tichauer JE, Eugenin J. Aging-dependent changes of microglial cells and their relevance for neurodegenerative disorders. J Neurochem. 2010; 112:1099–114. [PubMed: 20002526]

Wang S, Zhang J, Zeng X, Zeng Y, Chen S. Association of traffic-related air pollution with children’s neurobehavioral functions in Quanzhou, China. Environ Health Perspect. 2009; 117:1612–8. [PubMed: 20019914]

Weaver IC, Diorio J, Seckl JR, Szyf M, Meaney MJ. Early environmental regulation of hippocampal glucocorticoid receptor gene expression: characterization of intracellular mediators and potential genomic target sites. Ann N Y Acad Sci. 2004; 1024:182–212. [PubMed: 15265782]

Weaver IC, La Plante P, Weaver S, Parent A, Sharma S, Diorio J, et al. Early environmental regulation of hippocampal glucocorticoid receptor gene expression: characterization of intracellular mediators and potential genomic target sites. Mol Cell Endocrinol. 2001; 185:205–18. [PubMed: 11738810]

Weuve J, Puett RC, Schwartz J, Yanosky JD, Laden F, Grodstein F. Exposure to particulate air pollution and cognitive decline in older women. Arch Intern Med. 2012; 172:219–27. [PubMed: 22332151]

Whitsel EA, Quibrera PM, Christ SL, Liao D, Prineas RJ, Anderson GL, et al. Heart rate variability, ambient particulate matter air pollution, and glucose homeostasis: the environmental epidemiology of arrhythmogenesis in the women’s health initiative. Am J Epidemiol. 2009; 169:693–703. [PubMed: 19208727]

Willis AW, Evanoff BA, Lian M, Galarza A, Wegrzyn A, Schootman M, et al. Metal emissions and urban incident Parkinson disease: a community health study of Medicare beneficiaries by using geographic information systems. Am J Epidemiol. 2010; 172:1357–63. [PubMed: 20959505]

Win-Shwe TT, Fujimaki H. Neurotoxicity of toluene. Toxicol Lett. 2010; 198:93–9. [PubMed: 20599484]

Win-Shwe TT, Mitsushima D, Yamamoto S, Fujitani Y, Funabashi T, Hirano S, et al. Extracellular glutamate level and NMDA receptor subunit expression in mouse olfactory bulb following nanoparticle-rich diesel exhaust exposure. Inhal Toxicol. 2009; 21:828–36. [PubMed: 19653804]

Win-Shwe TT, Yamamoto S, Fujitani Y, Hirano S, Fujimaki H. Nanoparticle-rich diesel exhaust affects hippocampal-dependent spatial learning and NMDA receptor subunit expression in female mice. Nanotoxicology. 2011

Wirdefeldt K, Adami HO, Cole P, Trichopoulos D, Mandel J. Epidemiology and etiology of Parkinson's disease: a review of the evidence. Eur J Epidemiol. 2011; 26(Suppl 1):S1–58. [PubMed: 21626386]

Wright RJ. Health effects of socially toxic neighborhoods: the violence and urban asthma paradigm. Clin Chest Med. 2006; 27:413–21. v. [PubMed: 16880051]

Wu C, Morris JR. Genes, genetics, and epigenetics: a correspondence. Science. 2001; 293:1103–5. [PubMed: 11498582]

Wu J, Houston D, Lurmann F, Ong P, Winer A. Exposure of PM2.5 and EC from diesel and gasoline vehicles in communities near the Ports of Los Angeles and Long Beach, California. Atmos Environ. 2009a; 43:1962–71.

Wu J, Lurmann F, Winer A, Lu R, Turco R, Funk T. Development of an individual exposure model for application to the Southern California children's health study. Atmos Environ. 2005; 39:259–73.

Wu J, Ren C, Delfino R, Chung J, Wilhelm M, Ritz B. Association between local traffic-generated air pollution and preeclampsia and preterm delivery in the South Coast Air Basin of California. Environ Health Perspect. 2009b; 117:1773–9. [PubMed: 20049131]

Wu J, Wilhelm M, Chung J, Ritz B. Comparing exposure assessment methods for traffic-related air pollution in an adverse pregnancy outcome study. Environ Res. 2011; 111:685–92. [PubMed: 21453913]

Yenari MA, Kauppinen TM, Swanson RA. Microglial activation in stroke: therapeutic targets. Neurotherapeutics. 2010; 7:378–91. [PubMed: 20880502]

Yokota S, Mizuo K, Moriya N, Oshio S, Sugawara I, Takeda K. Effect of prenatal exposure to diesel exhaust on dopaminergic system in mice. Neurosci Lett. 2009; 449:38–41. [PubMed: 18938223]

Yokota S, Takashima H, Ohta R, Saito Y, Miyahara T, Yoshida Y, et al. Nasal instillation of nanoparticle-rich diesel exhaust particles slightly affects emotional behavior and learning capability in rats. J Toxicol Sci. 2011; 36:267–76. [PubMed: 21628955]

Zaehner T, Plueshke V, Frey BM, Frey FJ, Ferrari P. Structural analysis of the 11 beta-hydroxysteroid dehydrogenase type 2 gene in end-stage renal disease. Kindey International. 2000; 58:1413–9.

Zhang H, Liu H, Davies KJ, Sioutas C, Finch CE, Morgan TE, et al. Nrf2-regulated phase II enzymes are induced by chronic ambient nanoparticle exposure in young mice with age-related impairments. Free Radic Biol Med. 2012; 52:2038–46. [PubMed: 22401859]

Zhou Y, Levy JI. Factors influencing the spatial extent of mobile source air pollution impacts: a meta-analysis. BMC Public Health. 2007; 7:89. [PubMed: 17519039]

Zhu Y, Hinds WC, Kim S, Sioutas C. Concentration and size distribution of ultrafine particles near a major highway. J Air Waste Manag Assoc. 2002a; 52:1032–42. [PubMed: 12269664]

Zhu YF, Hinds WC, Kim S, Shen S, Sioutas C. Study of ultrafine particles near a major highway with heavy-duty diesel traffic. Atmospheric Environment. 2002b; 36:4323–35.