HHS Public Access

Author manuscript

Curr Environ Health Rep. Author manuscript; available in PMC 2018 June 01.

Published in final edited form as:

Curr Environ Health Rep. 2017 June ; 4(2): 180–191. doi:10.1007/s40572-017-0134-3.

Cognitive Effects of Air Pollution Exposures and Potential Mechanistic Underpinnings

J.L. Allen, Ph.D., **C. Klocke**, **K. Morris-Schaffer**, **K. Conrad**, **M. Sobolewski, Ph.D.**, and **D.A. Cory-Slechta, Ph.D.**[1]

Department of Environmental Medicine University of Rochester Medical Center Rochester, NY 14642

Abstract

Purpose of review—This review sought to address the potential for air pollutants to impair cognition and mechanisms by which that might occur.

Recent findings—Air pollution has been associated with deficits in cognitive functions across a wide range of epidemiological studies, both with developmental and adult exposures. Studies in animal models are significantly more limited in number, with somewhat inconsistent findings to date for measures of learning, but show more consistent impairments for short term memory. Potential contributory mechanisms include oxidative stress/inflammation, altered levels of dopamine and/or glutamate and changes in synaptic plasticity/structure.

Summary—Epidemiological studies are consistent with adverse effects of air pollutants on cognition, but additional studies and better phenotypic characterization are needed for animal models, including more precise delineation of specific components of cognition that are affected, as well as definitions of critical exposure periods for such effects and the components of air pollution responsible. This would permit development of more circumscribed hypotheses as to potential behavioral and neurobiological mechanisms.

Keywords

Air pollution; learning; memory; attention; inflammation; glutamate

I. INTRODUCTION

Air pollution is a worldwide environmental health problem. Such exposures can potentially begin during gestation, and can also be cumulative over the lifespan. As of 2013, air pollution was considered to be the 12th leading global risk factor for disability adjusted life year reductions (1), leading to 3.3 million premature deaths per year (2) in the Global

[1]**Corresponding author:** Box EHSC, University of Rochester Medical Center, Rochester, NY, 14642; deborah_cory-slechta@urmc.rochester.edu.

Conflict of Interest

J.L. Allen, C. Klocke, K. Morris-Schaffer, K. Conrad, M. Sobolewski, and D.A. Cory-Slechta declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Burden of Disease Study. Air quality standards have clearly improved in some countries, hopefully mitigating such trends, but even as of 2012, the U.S. Environmental Protection Agency (EPA) estimated that approximately 142 million U.S. residents still live in areas where levels of various air pollutants exceeded regulations. This is coupled with predictions of further increases in ongoing urbanization trends and expanding road traffic in many areas of the world which could further increase population exposures to air pollution (3).

Air pollution is a complex mixture that includes particles, oxidant gases (e.g., O_3, NO_x), trace metals, and adsorbed organic contaminants. Particulate matter (PM) sizes range from coarse (PM_{10}; <10μm) to fine ($PM_{2.5}$; <2.5μm) to ultrafine (<0.1μm). While not a significant component of air pollution by mass, ultrafine particles (UFPs) achieve orders of magnitude higher particle count concentrations and surface area compared to larger particle sizes. For both chemical and health reasons, UFPs are generally considered among the most reactive elements of air pollution (4, 5). Their high surface area permits greater adsorption of other toxic air pollutants per unit mass. Further, up to 50% of inhaled UFP is deposited in pulmonary alveolar regions of lung from, from which it can pass through the alveolocapillary barrier and thereby access pulmonary interstitium. From there, particles can cross endothelial cells, move into blood circulation and thus impact other organs, such as heart and brain, to produce more serious health consequences. This is coupled with data indicating deposition can also occur in the nasal cavity allowing translocation to brain directly across the olfactory epithelium (6, 7).

Currently, the U.S. EPA sets regulatory standards for levels of PM_{10} and $PM_{2.5}$. Based on some other observations, however, current regulations, while effective in reducing some components of air pollution, may not be sufficient. For example, studies have suggested that UFP levels may not necessarily be inferred from PM mass measurements (8, 9). Increases in levels of UFPs can actually be fostered by clean atmospheric conditions (10), and differences in fuel types also change UFP levels (11, 12). Although it represents a significant technological challenge, pressure for regulation of UFPs arises from the growing data base on associated health effects.

The focus of air pollution research has long been directed at cardiovascular and pulmonary systems. However, an increasing body of evidence is demonstrating that air pollution is also deleterious to the central nervous system (CNS). Human studies are now reporting associations of various components of air pollution and associated contaminants with neurodevelopmental disorders as well as with neurodegenerative diseases (13–16), and the mechanisms by which air pollution toxicity occurs in peripheral organs, including inflammation and oxidative stress, are also likely operative in the CNS (17). This review will summarize the current literature reporting cognitive-related deficits that have been described in relation to components of air pollution in both human epidemiological and experimental animal studies. It will then examine potential mechanisms by which such effects might occur as have also been reported for human and experimental animal exposures. It concludes by describing limitations of the current understanding and future directions for research.

Effects of Air Pollution on Cognitive Functions

Increasing evidence suggests that air pollution can produce neurotoxicity. Moreover, such effects are reported both in children and in adult stages of the life cycle, in both epidemiological and experimental animal model studies. Several reviews of such effects have already been reported (13–16, 18–22). Though human studies have used different measures of air pollution, and animal studies have employed differing air pollution exposures, many report impairments in cognitive function.

Studies of Cognition in Adults

Human epidemiological studies report deficits in various aspects of cognitive function in both cross-sectional and longitudinal assessments which have come from multiple different cohorts and locations. These have included reductions in test scores for mild cognitive impairment (MCI) in elderly women in Germany who had lived at the same address for more than 20 years (23). In a more recent follow up study of this population, levels of mono-nitrogen oxides (NO_x) were associated with a decline in a global test score across neuropsychological tests, and specific associations were seen between visuo-spatial abilities and NO_2, NO_x and PM_{10}, as well as the Boston Naming Test with NO_x (24). Another German cross-sectional cohort study of 50–80 yr olds found that long term exposures to $PM_{2.5}$ air pollution showed a positive association with reduced MCI (scores, particularly amnestic MCI components) (25). Levels of black carbon, a measure of traffic-related pollution were associated with lower Mini-Mental State Examination scores in a population of older men from the VA Normative Aging Study (26). Exposures to polycyclic aromatic hydrocarbons (PAHs), a class of chemicals present in particulate matter, was found to be negatively associated with digit symbol substitution test scores in a population 60 yrs of age and above from the National Health and Nutrition Examination Survey (27). In a national sample of older U.S. adults, $PM_{2.5}$ was associated with a 1.5 times higher error rate in a cognitive assessment task (28). Increased $PM_{2.5}$ levels were found to be associated with reduced verbal learning, and NO_2 with decreased logical memory in middle and older-aged Los Angeles adults (29).

Prospective studies offer the potential to assess rates of cognitive decline. For example, more rapid cognitive decline was reported in elderly U.S. women exposed from 7–14 years to $PM_{2.5–10}$ and $PM_{2.5}$ (30). Similarly, in a London cohort, levels of PM were associated with a decline in cognition over a 5 year period (31). In another prospective study, residential proximity to a major roadway impaired verbal learning and memory, psychomotor speed, language and executive functioning in Boston community-dwelling seniors (32).

Studies of Cognition in Children

In a prospective Boston cohort of children, living nearer a major roadway at birth was associated with lower nonverbal IQ and visual motor abilities at mid-childhood (33), although a subsequent study did not find that prenatal or early childhood exposure to traffic-related pollution was associated with impaired executive function at least as measured via parent and teacher rating scales (34). Children from Quanzhou, China exposed to higher levels of NO_2 and PM had reduced reaction times and impaired performance on the

continuous performance, digit symbol substitution, pursuit aiming and sign register tests (35). Higher black carbon levels in a prospective cohort study were shown to be predictive of decreased cognitive function, particularly verbal and nonverbal intelligence and memory function, in Boston children (36). NO_2 was found to be a predictor of decreased memory function in the delayed matching to sample test in 9–11 year old Dutch children (37). In a study spanning 6 European birth cohorts that assessed cognitive and psychomotor development between 1–6 yrs of age, it was found that maternal NO_2 exposure was associated with delayed psychomotor development during childhood (38). As with adults, PAHs were found to influence cognitive function via prenatal exposure, particularly verbal IQ, with postnatal exposures also increasing risk (39).

Exposures to higher levels of traffic were reported to reduce sustained attention in a study of Flemish adolescents (40). Similarly, in a case-control study, levels of PM_{10} in breathing air was found to be a major risk factor for attention deficit hyperactivity (ADHD) disorder in Delhi school children, particularly the inattentive type of ADHD (41). Exposure to elemental carbon during infancy was associated with higher hyperactivity scores in children whose mothers had more than a high school education (42). However, in a study of Swedish twins, neither NO_x or PM_{10} exposure during pregnancy was associated with ADHD (43).

With respect to time-based effects and or cumulative exposures, a prospective cohort study in 7–10 yr old primary school children from 39 schools in Barcelona observed a slower growth in cognitive development (working memory, and inattentiveness) over a 12 month trajectory, including 4 different time points of measurement was found in association to traffic-related air pollution (NO_2, UFP number and elemental carbon) (44), and was found to be due to traffic-related $PM_{2.5}$ (45). A prospective cohort study of South Korean children reported negative associations between maternal exposures to PM_{10} and both Mental Development and Psychomotor Development Index scores of the Bayley Scales of Infant Development throughout the first 24 mos of life (46).

Studies of Cognition in Experimental Animal Models

To date, significantly fewer studies have examined the impact of air pollution specifically on cognitive functions in experimental animal models. Correspondingly, the number of behavioral paradigms used has been limited, and evidence for specific effects on cognitive domains is not always clearly established. Furthermore, studies that have not used an inhalational route of exposure (e.g. intranasal instillation) may be of limited translational utility to human conditions. These studies are summarized in Table 1.

Of additional relevance to the experimental animal studies is the long held assertion that rodent models of inhaled air may not be fully relevant to humans in terms of exposure parameters, as rodents are obligate nose-breathers and as a result, dosing of mice will result in higher exposures than occur in humans. Recent findings, however, appear to contradict this concern, showing that the olfactory dose per unit surface area is actually estimated to be higher in humans depending on the size of the particle (47, 48), as based on computational modeling with an anatomically accurate model of the human nasal cavity. This may be particularly relevant considering a recent editorial (49) noting the presence in fly ash and car

exhaust of a significant fraction of particles below 10 nm, often overlooked because of measurement difficulty (50).

Diesel Exhaust Exposures and Cognition—To date, only two studies have specifically examined ***learning*** in response to diesel exhaust exposures, in both cases following maternal exposures. Inhalational exposure of mice to approximately 20 mg diesel exhaust particles/m^3 on gestational days (GD) 7–19 was reported not to impair learning in a water maze over the initial learning or memory trials, but to improve learning on the first trial of the first reversal (movement of the location of the escape platform) trials in adult female offspring, while males were not affected (51). In a study of subcutaneous exposures of mice to 200 ug/kg body weight diesel exhaust particle suspensions on gestational days 6, 9, 12, 15 and 18, adult male offspring (females not tested) were reported to show deficits in acquisition of water maze performance, as indicated by longer latencies to find the escape platform; however, significant effects were only found on one day, i.e. day 7 of the 9 days of behavioral testing (52). Two studies examined water maze learning in response to clean air or to nanoparticle-rich diesel exhaust. In the first (53), male mice were exposed to clean air or 148.86 ug/m^3 nanoparticle-rich diesel exhaust for 5 hr/day for 5 days/week for 4 weeks, but no effects on learning were observed. In another study, female mice were exposed to clean air or moderate (35.48 ug/m^3) or high concentrations (122 ug/m^3) of nanoparticle-rich diesel exhaust; in this case, only the high concentration significantly increased escape latencies during acquisition and in a reversal phase (54).

Two studies examined ***short-term memory*** effects of diesel exhaust using the novel object recognition paradigm in mice. Adult female mice exposed to high concentrations (122 ug/m^3) of nanoparticle-rich diesel exhaust for 3 months showed an impaired discrimination index for novel object recognition with no differences in object exploration time during training, consistent with impaired short-term memory, relative to clean air or moderately (35.48 ug/m^3)-exposed groups (55). In a second study, adult male mice were exposed to diesel engine exhaust or diesel exhaust origin secondary organic aerosols produced by addition of ozone for 5 hr/day for 5 days/week for one or three months; concentrations of diesel exhaust were 98 ug/m^3 and diesel exhaust with generated secondary organic aerosols was 114 ug/m^3. Diesel exhaust with generated secondary organic aerosols reduced exploration time with the novel object, again without altering object exploration time during training after both 1 and 3 months of exposure (56).

Particulate Matter (PM) Exposures and Cognition—Four week old male mice exposed to concentrated ambient air ($PM_{2.5}$; 94.3 ug/m^3) or filtered air for 6 hr per day, 5 days per week for approximately 10 months underwent assessment of ***learning*** in a Barnes maze. Latency to find the escape hole in the maze was reported to be significantly increased by $PM_{2.5}$, although this effect was only statistically significant for day 2 of the 4 days of training (as based on analysis by one way rather than repeated measures ANOVA). Number of errors on the maze (wrong escape hole attempts) were also increased by $PM_{2.5}$ during session 2 of training (57).

Studies from our laboratory have examined the impact of developmental and/or adult exposures to concentrated ambient UFP. In one such study, exposures that ranged from 3.33

to 21.5 times that of ambient outdoor air, at 15–240 ug/m^3, or to filtered air, were carried out in mice for 4 hr/day from postnatal days 4–7 and 10–13 (developmental exposure) and/or from postnatal days 56–59 (adult exposure) (58). Learning was measured using a fixed interval (FI) schedule of food reward to determine acquisition of characteristic performance on this schedule. Developmental exposures to UFP significantly retarded acquisition of FI performance in males, significantly decreasing rates of responding. In contrast, adult exposures resulted in marked increases in FI response rates in females. As only a single response is required to produce food reward on the FI schedule, both patterns of responding (decreased and increased response rates) represent altered learning. Potential for impulsivity, a component of attention deficit hyperactivity disorder was also investigated using a fixed ratio (FR) waiting for reward paradigm (59), which provided free reward deliveries with an increasing waiting time between each such delivery after mice had completed a ratio of 25 lever press responses in an operant chamber. Any responses during the waiting period of free reward deliveries reset the FR requirement for another 25 responses. Under these conditions, developmentally-exposed males (females not yet tested) showed a significant increase in numbers of FR resets and a significantly shorter mean waiting time; this also resulted in a significantly larger number of responses being required for each reward delivery.

Two studies have examined PM exposure effects on ***short-term memory***. Male rats were exposed to ambient $PM_{2.5}$ air pollution and/or filtered air from prenatal-weaning periods and through adulthood to 150 days of age (60), with a total monthly $PM_{2.5}$ mass cited of 16.2 ug/m^3. At 151 days, short term memory was assessed using a spontaneous nonmatching to sample recognition test which is analogous to novel object recognition. Significant reduction in short-term memory as indicated by the discrimination index were seen in the group exposed from gestation throughout adulthood to $PM_{2.5;}$ this group also exhibited less exploration time during the test session for memory of the novel object. Short-term memory was also assessed in the study cited above from our laboratory that utilized developmental and/or adult exposures to concentrated ambient UFP (58). Developmental UFP exposures reduced time in contact with the novel object in both males and females, findings again consistent with a short-term memory impairment.

Potential Mechanisms of Cognitive Impairment

With the limited number of experimental animal studies to date that have focused on the cognitive consequences of air pollution, neurotoxicological mechanisms of impairment obviously have yet to be identified. There are, however several neuropathological and neurobiological changes that have been reported in experimental animal models that could be considered risk factors for cognitive impairment. These include microglial activation and inflammation, white matter damage, changes in dopamine and glutamate neurotransmitter systems and altered synaptic plasticity (17, 61).

In defining mechanisms, several considerations need to be recognized. Mechanisms are likely to differ depending upon the specific nature of the cognitive impairment. They are also highly likely to differ based upon the developmental period of exposure reflecting the aspects of brain development underway during the period of exposure. Mechanisms will also likely differ depending upon the components of the air pollution exposure itself. Given well

known differences in brain development, mechanisms are highly likely to show sex-dependence, as with other effects of air pollution. Finally, based on the systems-level mediation of cognitive functions by the brain, putative mechanisms may be inter-related, and differentiating proximal from system-based mechanistic effects could prove difficult.

For example, brain microglial activation results in the release of soluble factors that can include pro-inflammatory cytokines and free radicals, promoting oxidative stress. This can impair glutamate uptake by glial cells and reduce the expression of glutamate transporters by glial cells. Excess glutamate can produce both neuronal and white matter damage. Oligodendrocytes, the myelinating cells of the brain, are particularly susceptible to glutamate toxicity (62), which can lead to myelination damage to developing white matter, as well as to microglial activation which could result in hypomyelination (63), for example. Glutamate release, moreover can further activate microglia (64–66). Microglial activation itself can damage the oligodendrocytes and thus lead to white matter loss (67). Sex-dependence of the colonization of brain by microglia and their activation profiles have been shown (68).

Microglial Activation/Inflammation/Oxidative Stress and White Matter Damage

Microglial function contributes to learning and memory processes across the lifespan, including via their roles in regulating neuronal structure and function (69), and to levels of inflammation and oxidative stress (70). White matter damage that can result from loss of or failure of development of myelin can also be a mediator of cognitive dysfunction not only in adults (71) but also during development (72).

Markers of microglial activation, inflammation and oxidative stress have been noted in response to both diesel exhaust and PM exposures in animal models. With respect to diesel exhaust, for example, even an acute (250–300 ug/m^3) exposure of 6 hours in adult mice led to microglial activation. It also increased lipid peroxidation and produced neuroinflammation that was most pronounced in hippocampus and olfactory bulb. Notably, effects were of greater magnitude in males (13). Following a 4 week, 5 days per week for 6 hr a day nose-only exposure of rats to diesel exhaust, levels of proinflammatory cytokines TNF-α and IL-1α were increased in striatum, although not in other brain regions examined (73). A 4 week exposure of adult rats to diesel exhaust increased TNA-α, IL1-6 and MIP-1a in olfactory bulb, cortex and midbrain, while increases in IL-1α were found in cortex and midbrain, and increases in the microglial marker IBA-1 were found in midbrain (74). In *in vitro* models, diesel exhaust was shown to increase oxidative stress markers in microglia (75).

PM exposures likewise appear to provoke microglial activation, inflammation and oxidative stress. Mice exposed developmentally to concentrated ambient UFP in our studies showed male-specific increases in IBA-1 in anterior commissure at postnatal day (PND) 14, and at PND55 in hippocampus (76, 77), and marked increases in corpus callosum when measured at PND270, regardless of whether exposure was during development, as adults, or both (58). Exposure of male rats to PM from pre-natal through adulthood increased cortical levels of the oxidative stress marker malondialdehyde and reduced levels of [superoxide dismutase]/[catalase] (60). In a study of ambient PM_{10} exposure in rats, increases in cortical levels of

IL-1β, iNOS, COX-2, ICAM-1 were found along with increases in TUNEL staining (78). Exposures of adult mice to re-aerosolized nanoPM increased levels of TNF-α, 4+NHe and 3-NT in olfactory epithelium and levels of IBA-1 in olfactory epithelium and olfactory bulb (79).

Changes in white matter structures have also been reported in response to ambient PM exposures, both in human and animal studies. In a prospective study, over 1400 community dwelling older women without dementia underwent MRI scans between 71–89 years of age. Those with greater $PM_{2.5}$ exposures had significant reductions in white matter, regardless of geographic region, socioeconomic status, lifestyle, or cardiovascular risk factors (80). These effects were found in the frontal and temporal cortical lobes as well as in corpus callosum, but not in hippocampus. In another recent study, MRI assessments of 263 children between 8–12 years of age reported that greater exposures to air pollution (as indicated by elemental carbon and NO_2) was associated with higher levels of functional connectivity between the dorsal frontal and parietal cortex regions, but with lower functional connectivity between dorsal frontal and medial frontal cortex, changes that were also associated with reaction time/motor speed, although not with the cognitive tasks used (81). PAHs, an organic contaminant of air pollution were reported to be associated with significant reductions in white matter surface confined almost entirely to the left hemisphere in children 7–9 years of age, and these correlated with slower information processing speed in intelligence tests as well as with behavioral problems such as attention deficit-related behaviors and conduct disorders (82).

Mice exposed developmentally to concentrated ambient UFP in our studies show persistent male-specific ventriculomegaly (an indicator of white matter damage) which were still observed at PND270. In addition, corresponding male-specific reductions in size of the corpus callosum and myelination of the corpus callosum were found, with these changes still evident at PND55, but resolving by PND 270 (76, 77).

Dopamine and Glutamate System Alternations

Dopamine and glutamate systems are overlapping neurotransmitter systems critical to mediation of cognitive functions (83, 84); both play a role in proliferation, differentiation and ultimately myelination by oligodendrocytes (62). Numerous studies have examined the impact of diesel exhaust exposure on neurotransmitter functions, while fewer studies to date have examined such changes in response to PM exposures.

Effects of diesel exhaust exposure on glutamatergic functions have been reported but the pattern of changes have not been consistent. Several studies examined the effects of diesel exhaust inhalational exposures on mRNA levels of glutamatergic receptors. In a study of diesel exhaust exposure of mice from GD14 to PND21, glutamate concentrations in hypothalamus were increased to the same extent by diesel exhaust alone and in conjunction with secondary organic aerosols (85). In a study of diesel injected subcutaneously at GD 6, 9, 12, 15 and 18, a slight reduction was found in NR2A receptor mRNA in hippocampus in offspring at 10 weeks of age (52). Following a 4 week inhalational exposure of adolescent male mice, increased levels of hippocampal NR1, NR2A and NR2B receptors were seen in mice (53). A study of adolescent male mice that involved a 1 or 3 mos inhalation exposure

of males to diesel exhaust or diesel exhaust plus secondary organic aerosols reported changes in mRNA levels of NR1, NR2A and NR2B receptors only in the diesel exhaust and secondary organic aerosols condition (56). Whereas a 3 mos exposure of female mice beginning in adolescence produced no changes in NMDA receptor subunits, but decreased levels of the glutamate transporter EAAT4 in hippocampus (86), a study with highly comparable exposures, again in females, found increases in levels of mRNA NR2A expression at the higher dose in hippocampus (54). Interestingly, the major difference between these latter two studies was the difference in behavioral history of the females, one group having been subjected to water maze testing, and the other to novel object recognition testing. Given our studies indicating behavioral experience can have a major impact on the trajectory of CNS effects of toxicants such as lead and methylmercury, we have deemed it critical to include non-behaviorally-tested control animals in all such studies (87, 88).

With respect to dopamine, prenatal diesel exhaust inhalational exposures from GD2-17 were found to decrease levels of the dopamine metabolite homovanillic acid (HVA) in nucleus accumbens, and dopamine turnover in striatum and nucleus accumbens (89). Using the same exposure protocol, a subsequent study by this group reported reductions in dopamine in prefrontal cortex, but transient increases in dopamine and its metabolites in amygdala that were evident at 3 weeks but not 6 weeks later (90). Inhalation exposure to diesel exhaust from GD2-17 increased dopamine and metabolites in prefrontal cortex and nucleus accumbens, but not in amgydala or ventral tegmental area (91). In another inhalational study, exposures from GD2-16 found increased dopamine and metabolites in prefrontal cortex, but decreased dopamine and some metabolites in midbrain and brain stem; alterations in dopamine turnover were found in striatum (92).

PM exposures likewise appear to alter both neurotransmitter systems. In our studies of mice exposed developmentally (human third trimester equivalent) to concentrated ambient UFPs, increases in glutamate were seen at PND14 and PND55 in hippocampus (only region examined) in male and female offspring (76). With the same exposure protocol, however, measures at approximately PND75 showed increased glutamate and glutamate turnover in striatum and decreased glutamine and increased glutamate turnover in hypothalamus (93). In assessments carried out at PND270, increases in glutamate and glutamine were seen in frontal cortex of males and females, while increases in hippocampus were seen only in males (58). A time course assessment in prefrontal cortex of PND14 and PND60 showed male-specific increases in the ratio of [glutamate]/[GABA], consistent with excitatory/inhibitory imbalance (77). Chronic inhalation of re-aerosolized nanoparticulate matter in mice reduced levels of the glutamate receptor subunit GluA1 in hippocampus; in hippocampal slice preparations, nanoparticulate matter suspensions increased the neurotoxicity of the glutamatergic agonist NMDA (94). In further support of glutamatergic involvement, male mice exposed developmentally to concentrated ambient UFP showed increased levels of glial fibrillary acidic protein (GFAP), a marker of astrocytic activation in amygdala at PND14 (93) and in frontal cortex of females even at PND270 (58). Astrocytes, as part of tripartite synapses, are critically involved in glutamate regulation and consequent modulation of synaptic plasticity (95).

Increased prefrontal cortex and midbrain dopamine were found at PND14 and PND55 in males, while females showed increased dopamine turnover in prefrontal cortex, and increases in dopamine and HVA, but decreases in dopamine turnover in midbrain in our studies of concentrated ambient UFP exposures during development (76). Using the same exposures, male mice (females not examined) sacrificed at approximately PND75 showed increases in the dopamine metabolite DOPAC and increased dopamine turnover in striatum, but decreases in midbrain, and reduced HVA in prefrontal cortex (93). Further, mice sacrificed at PND270 were found to have dopamine system alterations in striatum, frontal cortex, olfactory bulb, midbrain and hypothalamus, while alterations in females were seen in frontal cortex, hippocampus, olfactory bulb, hypothalamus and striatum (58).

Effects on Neuronal Markers

To date, changes in neuronal structure/function have received less examination as potential mechanisms of air pollution-induced cognitive deficits, but some studies are suggestive. For example, male mice exposed to $PM_{2.5}$ for 10 months showed decreased dendritic spine density and dendritic branching in hippocampal areas CA1 and CA3, respectively, changes that could influence learning and/or memory (57). In neonatal cerebral cortical neurons derived after prenatal exposures to re-aerosolized urban air nanoparticles, impaired differentiation was found, including a marked reduction in neurons with long neurites, indicating more undifferentiated neurons (96). In a follow-up study (97), the inhibition of neurite outgrowth was found to be caused by TNF-α from microglia. In an assessment of inhaled sulfur dioxide, a ubiquitous air pollutant, inhibition of mRNA levels of the synaptic plasticity marker Arc after both 1 and 4 weeks of exposure was observed, while protein expression of the presynaptic marker synaptophysin was reduced after 1 week of exposure.

Conclusions

Evidence of cognitive deficits in response to components of air pollution in human studies, even with the individual strengths and limitations of the reported studies, has become more compelling. Deficits in learning and memory as well as in attention-related behaviors are being reported, all of which can impair executive-type functions. Further, these reports are coming from different cohorts and from different geographical areas. Findings reported to date also suggest that adverse effects on cognition are not limited to developmental exposures, but may also be found in adults. While the reported evidence has increased, however, it is unclear whether any publication bias may have affected this data base.

As of yet, only a very limited number of studies to date have examined cognition in experimental animal studies, and these too have both strengths and weaknesses. Studies of learning that have followed diesel exhaust exposures appear, to date, to be inconsistent, with reports of both positive (detrimental) effects and of no effects, based on a single paradigm, the water maze. Studies based on PM exposures, although currently limited to 3 reports, do provide consistent evidence of learning impairments. Detrimental effects on short term memory following diesel exposure are consistently observed, although as of yet, this has been in a single behavioral paradigm and in only two studies, while such decrements have also been reported in studies based on PM exposures using the same behavioral paradigm in

two different studies. Thus, to date, experimental animal studies provide plausibility for short term memory effects of air pollution exposures.

Although numerous studies have examined potential underlying mechanisms by which air pollution may act on brain, such an assessment remains at its infancy. Few studies have examined brain changes in a direct mechanistic capacity in relation to specific behavioral functions, including cognitive deficits. In addition, as the brain represents a system of systems, with differential impacts on different cognitive functions, it may well be the case that multiple mechanisms are at play, and certainly that interactive mechanisms are occurring. It will, however, be critical for future studies to include non-behavioral controls in any assessments of mechanisms of air-pollution induced cognitive deficits, as behavioral experience itself will change brain functions, and can even serve in an ‘enrichment’ capacity to mitigate potential underlying mechanisms (87, 88).

Recognizing that there are numerous limitations to research, there are nevertheless multiple future research directions that would advance our understanding of the impacts of air pollution on cognition. In human studies, for example, it would be particularly useful to more specifically ascertain the impact of developmental period of exposure, as well as to more precisely characterize the specific behavioral domains of cognitive function that are being impacted. The former is particularly relevant to risk assessment, and the latter would be particularly important for devising any behavioral intervention procedures that might be used to overcome deficits. In addition, longer term prospective studies, particularly in adults would serve to further understand whether cognitive deficits are relevant to neurodegenerative conditions, particularly those that include a dementia component. Studies incorporating approaches such as imaging, including functional imaging, would yield insights into brain mechanisms and pathology and their similarity to findings from animal models. Of course, such a list always includes the need for further assessment of the specific components of air pollution that lead to such effects. That information would be pertinent to air quality criteria regulations as well as to defining underlying mechanisms.

With respect to experimental animal models, additional assessments of cognitive function are needed, given the limited data base currently available. It would be useful if that included not only characterization of different components of cognition (e.g., learning, memory, attention), but also multiple different measures of each of those components. Such assessments would assist in further defining the extent/nature and context of such deficits, as well as their behavioral mechanisms of action (98, 99). More definitive phenotyping would also assist in circumscribing future studies of neurobiological mechanisms of action for cognitive impairments. Once hypotheses can be more fully developed, the use of genetically engineered animal models may be of potential use. As with human studies, delineation of critical periods of exposure and their potential to produce different phenotypes is as yet unclear. Future research here would also benefit from additional information as to the critical components of air pollution in producing cognitive deficits and to the use of inhalational exposures.

References

Papers of particular interest, published recently, have been highlighted as:

•Of importance

••Of outstanding importance

1. Forouzanfar MH, Alexander L, Anderson HR, Bachman VF, Biryukov S, Brauer M, et al. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990–2013 a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015; :2287–323. DOI: 10.1016/S0140-6736(15)00128-2 [PubMed: 26364544]
2. Lelieveld J, Evans JS, Fnais M, Giannadaki D, Pozzer A. The contribution of outdoor air pollution sources to premature mortality on a global scale. Nature. 2015; 525(7569):367–71. DOI: 10.1038/nature15371 [PubMed: 26381985]
3. Kumar P, Morawska L, Birmili W, Paasonen P, Hu M, Kulmala M, et al. Ultrafine particles in cities. Environ Int. 2014; 66:1–10. DOI: 10.1016/j.envint.2014.01.013 [PubMed: 24503484]
4. Oberdorster G, Ferin J, Lehnert BE. Correlation between particle size, in vivo particle persistence, and lung injury. Environ Health Perspect. 1994; 102(Suppl 5):173–9.
5. Brown DM, Wilson MR, MacNee W, Stone V, Donaldson K. Size-dependent proinflammatory effects of ultrafine polystyrene particles: a role for surface area and oxidative stress in the enhanced activity of ultrafines. Toxicol Appl Pharmacol. 2001; 175(3):191–9. DOI: 10.1006/taap.2001.9240 [PubMed: 11559017]
6. 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(8):1172–8. [PubMed: 16882521]
7. 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(1):113–23. DOI: 10.1016/j.neuro.2004.06.005 [PubMed: 15527879]
8. Ruuskanen J, Tuch T, Brink T, Peters A, Khlystov A, Mirme A, et al. Concentrations of ultrafine, fine and PM2.5 particles in three European cities. Atmos Environ. 2001; 35:3729–8.
9. Pitz M, Kreyling WG, Holscher B, Cyrys J, Wichmann HE, Heinrich J. Change of the ambient particle size distribution in East Germany between 1993 and 1999. Atmos Environ. 2001; 35(25):4357–66. DOI: 10.1016/S1352-2310(01)00229-1
10. Martins LD, Martins JA, Freitas ED, Mazzoli CR, Goncalves FLT, Ynoue RY, et al. Potential health impact of ultrafine particles under clean and polluted urban atmospheric conditions: a model-based study. Air Quality Atmosphere and Health. 2010; 3(1):29–39. DOI: 10.1007/s11869-009-0048-9
11. Frank BP, Tang S, Lanni T, Grygas J, Rideout G, Meyer N, et al. The effect of fuel type and aftertreatment method on ultrafine particle emissions from a heavy-duty diesel engine. Aerosol Science and Technology. 2007; 41(11):1029–39. DOI: 10.1080/02786820701697531
12. Ristovski ZD, Jayaratne ER, Lim M, Ayoko GA, Morawska L. Influence of diesel fuel sulfur on nanoparticle emissions from city buses. Environmental Science & Technology. 2006; 40(4):1314–20. DOI: 10.1021/es050094i [PubMed: 16572791]
13. Costa LG, Cole TB, Coburn J, Chang YC, Dao K, Roque PJ. Neurotoxicity of traffic-related air pollution. Neurotoxicology. 2015; doi: 10.1016/j.neuro.2015.11.008
14. Heusinkveld HJ, Wahle T, Campbell A, Westerink RH, Tran L, Johnston H, et al. Neurodegenerative and neurological disorders by small inhaled particles. Neurotoxicology. 2016; 56:94–106. DOI: 10.1016/j.neuro.2016.07.007 [PubMed: 27448464]
15. Power MC, Adar SD, Yanosky JD, Weuve J. Exposure to air pollution as a potential contributor to cognitive function, cognitive decline, brain imaging, and dementia: A systematic review of epidemiologic research. Neurotoxicology. 2016; doi: 10.1016/j.neuro.2016.06.004

16. Xu X, Ha SU, Basnet R. A Review of Epidemiological Research on Adverse Neurological Effects of Exposure to Ambient Air Pollution. Front Public Health. 2016; 4:157.doi: 10.3389/fpubh.2016.00157 [PubMed: 27547751]

17•. Block ML, Calderon-Garciduenas L. Air pollution: mechanisms of neuroinflammation and CNS disease. Trends Neurosci. 2009; 32(9):506–16. Review of potential peripheral and CNS mechanisms of air pollution-induced neurotoxicity. DOI: 10.1016/j.tins.2009.05.009 [PubMed: 19716187]

18. Clifford A, Lang L, Chen R, Anstey KJ, Seaton A. Exposure to air pollution and cognitive functioning across the life course–A systematic literature review. Environ Res. 2016; 147:383–98. DOI: 10.1016/j.envres.2016.01.018 [PubMed: 26945620]

19. Guxens M, Sunyer J. A review of epidemiological studies on neuropsychological effects of air pollution. Swiss Med Wkly. 2012; 141:w13322.doi: 10.4414/smw.2011.13322 [PubMed: 22252905]

20. Peters R, Peters J, Booth A, Mudway I. Is air pollution associated with increased risk of cognitive decline? A systematic review. Age Ageing. 2015; 44(5):755–60. DOI: 10.1093/ageing/afv087 [PubMed: 26188335]

21. Suades-Gonzalez E, Gascon M, Guxens M, Sunyer J. Air Pollution and Neuropsychological Development: A Review of the Latest Evidence. Endocrinology. 2015; :en20151403.doi: 10.1210/en.2015-1403

22. Woodward N, Finch CE, Morgan TE. Traffic-related air pollution and brain development. AIMS Environ Sci. 2015; 2(2):353–73. DOI: 10.3934/environsci.2015.2.353 [PubMed: 27099868]

23. 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(8):1004–11. DOI: 10.1016/j.envres.2009.08.003 [PubMed: 19733348]

24. Schikowski T, Vossoughi M, Vierkotter A, Schulte T, Teichert T, Sugiri D, et al. Association of air pollution with cognitive functions and its modification by APOE gene variants in elderly women. Environ Res. 2015; 142:10–6. DOI: 10.1016/j.envres.2015.06.009 [PubMed: 26092807]

25. Tzivian L, Dlugaj M, Winkler A, Weinmayr G, Hennig F, Fuks KB, et al. Long-Term Air Pollution and Traffic Noise Exposures and Mild Cognitive Impairment in Older Adults: A Cross-Sectional Analysis of the Heinz Nixdorf Recall Study. Environ Health Perspect. 2016; 124(9):1361–8. DOI: 10.1289/ehp.1509824 [PubMed: 26863687]

26. Colicino E, Wilson A, Frisardi MC, Prada D, Power MC, Hoxha M, et al. Telomere Length, Long-Term Black Carbon Exposure, and Cognitive Function in a Cohort of Older Men: The VA Normative Aging Study. Environ Health Perspect. 2016; doi: 10.1289/EHP241

27. Best EA, Juarez-Colunga E, James K, LeBlanc WG, Serdar B. Biomarkers of Exposure to Polycyclic Aromatic Hydrocarbons and Cognitive Function among Elderly in the United States (National Health and Nutrition Examination Survey: 2001–2002). PLoS One. 2016; 11(2):e0147632.doi: 10.1371/journal.pone.0147632 [PubMed: 26849365]

28. Ailshire JA, Clarke P. Fine particulate matter air pollution and cognitive function among U.S. older adults. J Gerontol B Psychol Sci Soc Sci. 2015; 70(2):322–8. DOI: 10.1093/geronb/gbu064 [PubMed: 24906394]

29. Gatto NM, Henderson VW, Hodis HN, St John JA, Lurmann F, Chen JC, et al. Components of air pollution and cognitive function in middle-aged and older adults in Los Angeles. Neurotoxicology. 2014; 40:1–7. DOI: 10.1016/j.neuro.2013.09.004 [PubMed: 24148924]

30•. 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(3):219–27. Epidemiological study across 7–14 years showing that a 10 ug/m^3 increase in long-term PM exposure is the cognitive aging equivalent of approximately 2 years. DOI: 10.1001/archinternmed.2011.683 [PubMed: 22332151]

31. Tonne C, Elbaz A, Beevers S, Singh-Manoux A. Traffic-related air pollution in relation to cognitive function in older adults. Epidemiology. 2014; 25(5):674–81. DOI: 10.1097/EDE.0000000000000144 [PubMed: 25036434]

32. Wellenius GA, Boyle LD, Coull BA, Milberg WP, Gryparis A, Schwartz J, et al. Residential proximity to nearest major roadway and cognitive function in community-dwelling seniors: results

from the MOBILIZE Boston Study. J Am Geriatr Soc. 2012; 60(11):2075–80. DOI: 10.1111/j.1532-5415.2012.04195.x [PubMed: 23126566]

33. Harris MH, Gold DR, Rifas-Shiman SL, Melly SJ, Zanobetti A, Coull BA, et al. Prenatal and Childhood Traffic-Related Pollution Exposure and Childhood Cognition in the Project Viva Cohort (Massachusetts, USA). Environ Health Perspect. 2015; 123(10):1072–8. DOI: 10.1289/ehp.1408803 [PubMed: 25839914]
34. Harris MH, Gold DR, Rifas-Shiman SL, Melly SJ, Zanobetti A, Coull BA, et al. Prenatal and childhood traffic-related air pollution exposure and childhood executive function and behavior. Neurotoxicol Teratol. 2016; doi: 10.1016/j.ntt.2016.06.008
35. Wang S, Zhang J, Zeng X, Zeng Y, Wang S, Chen S. Association of traffic-related air pollution with children's neurobehavioral functions in Quanzhou, China. Environ Health Perspect. 2009; 117(10):1612–8. DOI: 10.1289/ehp.0800023 [PubMed: 20019914]
36. 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(3):280–6. DOI: 10.1093/aje/kwm308 [PubMed: 18006900]
37. van Kempen E, Fischer P, Janssen N, Houthuijs D, van Kamp I, Stansfeld S, et al. Neurobehavioral effects of exposure to traffic-related air pollution and transportation noise in primary schoolchildren. Environ Res. 2012; 115:18–25. DOI: 10.1016/j.envres.2012.03.002 [PubMed: 22483436]
38. Guxens M, Garcia-Esteban R, Giorgis-Allemand L, Forns J, Badaloni C, Ballester F, et al. Air pollution during pregnancy and childhood cognitive and psychomotor development: six European birth cohorts. Epidemiology. 2014; 25(5):636–47. DOI: 10.1097/EDE.0000000000000133 [PubMed: 25036432]
39. Jedrychowski WA, Perera FP, Camann D, Spengler J, Butscher M, Mroz E, et al. Prenatal exposure to polycyclic aromatic hydrocarbons and cognitive dysfunction in children. Environ Sci Pollut Res Int. 2015; 22(5):3631–9. DOI: 10.1007/s11356-014-3627-8 [PubMed: 25253062]
40. Kicinski M, Vermeir G, Van Larebeke N, Den Hond E, Schoeters G, Bruckers L, et al. Neurobehavioral performance in adolescents is inversely associated with traffic exposure. Environ Int. 2015; 75:136–43. DOI: 10.1016/j.envint.2014.10.028 [PubMed: 25461422]
41. Siddique S, Banerjee M, Ray MR, Lahiri T. Attention-deficit hyperactivity disorder in children chronically exposed to high level of vehicular pollution. Eur J Pediatr. 2011; 170(7):923–9. DOI: 10.1007/s00431-010-1379-0 [PubMed: 21191614]
42. Newman NC, Ryan P, Lemasters G, Levin L, Bernstein D, Hershey GK, et al. Traffic-related air pollution exposure in the first year of life and behavioral scores at 7 years of age. Environ Health Perspect. 2013; 121(6):731–6. DOI: 10.1289/ehp.1205555 [PubMed: 23694812]
43. Gong T, Almqvist C, Bolte S, Lichtenstein P, Anckarsater H, Lind T, et al. Exposure to air pollution from traffic and neurodevelopmental disorders in Swedish twins. Twin Res Hum Genet. 2014; 17(6):553–62. DOI: 10.1017/thg.2014.58 [PubMed: 25229653]
44. Sunyer J, Esnaola M, Alvarez-Pedrerol M, Forns J, Rivas I, Lopez-Vicente M, et al. Association between traffic-related air pollution in schools and cognitive development in primary school children: a prospective cohort study. PLoS Med. 2015; 12(3):e1001792.doi: 10.1371/journal.pmed.1001792 [PubMed: 25734425]
45•. Basagana X, Esnaola M, Rivas I, Amato F, Alvarez-Pedrerol M, Forns J, et al. Neurodevelopmental Deceleration by Urban Fine Particles from Different Emission Sources: A Longitudinal Observational Study. Environ Health Perspect. 2016; 124(5) Epidemiological study reporting that even an increase of an interquartile range in indoor traffic-related $PM_{2.5}$ was associated with reductions in cognitive growth, working memory and inattentiveness that ranged from 11–30 %. doi: 10.1289/EHP209
46. Kim E, Park H, Hong YC, Ha M, Kim Y, Kim BN, et al. Prenatal exposure to PM(1)(0) and NO(2) and children's neurodevelopment from birth to 24 months of age: mothers and Children's Environmental Health (MOCEH) study. Sci Total Environ. 2014; 481:439–45. DOI: 10.1016/j.scitotenv.2014.01.107 [PubMed: 24631606]
47. Dong J, Shang Y, Inthavong K, Tu J, Chen R, Bai R, et al. From the Cover: Comparative Numerical Modeling of Inhaled Nanoparticle Deposition in Human and Rat Nasal Cavities. Toxicol Sci. 2016; 152(2):284–96. DOI: 10.1093/toxsci/kfw087 [PubMed: 27208081]

48. Garcia GJ, Schroeter JD, Kimbell JS. Olfactory deposition of inhaled nanoparticles in humans. Inhal Toxicol. 2015; 27(8):394–403. DOI: 10.3109/08958378.2015.1066904 [PubMed: 26194036]
49. Pedata P, Stoeger T, Zimmermann R, Peters A, Oberdorster G, D'Anna A. Are we forgetting the smallest, sub 10 nm combustion generated particles? Particle and Fibre Toxicology. in press.
50. Ronkko T, Virtanen A, Kannosto J, Keskinen J, Lappi M, Pirjola L. Nucleation mode particles with a nonvolatile core in the exhaust of a heavy duty diesel vehicle. Environmental Science and Technology. 2007; 41:6384–9. [PubMed: 17948783]
51. Hougaard KS, Jensen KA, Nordly P, Taxvig C, Vogel U, Saber AT, et al. Effects of prenatal exposure to diesel exhaust particles on postnatal development, behavior, genotoxicity and inflammation in mice. Part Fibre Toxicol. 2008; 5:3.doi: 10.1186/1743-8977-5-3 [PubMed: 18331653]
52. Yokota S, Sato A, Umezawa M, Oshio S, Takeda K. In utero exposure of mice to diesel exhaust particles affects spatial learning and memory with reduced N-methyl-D-aspartate receptor expression in the hippocampus of male offspring. Neurotoxicology. 2015; 50:108–15. DOI: 10.1016/j.neuro.2015.08.009 [PubMed: 26291742]
53. Win-Shwe TT, Yamamoto S, Fujitani Y, Hirano S, Fujimaki H. Spatial learning and memory function-related gene expression in the hippocampus of mouse exposed to nanoparticle-rich diesel exhaust. Neurotoxicology. 2008; 29(6):940–7. DOI: 10.1016/j.neuro.2008.09.007 [PubMed: 18926851]
54. 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. 2012; 6(5):543–53. DOI: 10.3109/17435390.2011.590904 [PubMed: 21663545]
55. Win-Shwe TT, Fujimaki H, Fujitani Y, Hirano S. Novel object recognition ability in female mice following exposure to nanoparticle-rich diesel exhaust. Toxicol Appl Pharmacol. 2012; 262(3): 355–62. DOI: 10.1016/j.taap.2012.05.015 [PubMed: 22659509]
56. Win-Shwe TT, Fujitani Y, Kyi-Tha-Thu C, Furuyama A, Michikawa T, Tsukahara S, et al. Effects of diesel engine exhaust origin secondary organic aerosols on novel object recognition ability and maternal behavior in BALB/c mice. Int J Environ Res Public Health. 2014; 11(11):11286–307. DOI: 10.3390/ijerph111111286 [PubMed: 25361045]
57. 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(10):987–95. 73. DOI: 10.1038/mp.2011.76 [PubMed: 21727897]
58. Allen JL, Liu X, Weston D, Prince L, Oberdorster G, Finkelstein JN, et al. Developmental exposure to concentrated ambient ultrafine particulate matter air pollution in mice results in persistent and sex-dependent behavioral neurotoxicity and glial activation. Toxicol Sci. 2014; 140(1):160–78. DOI: 10.1093/toxsci/kfu059 [PubMed: 24690596]
59. Allen JL, Conrad K, Oberdorster G, Johnston CJ, Sleezer B, Cory-Slechta DA. Developmental exposure to concentrated ambient particles and preference for immediate reward in mice. Environ Health Perspect. 2013; 121(1):32–8. DOI: 10.1289/ehp.1205505 [PubMed: 23063827]
60. Zanchi AC, Fagundes LS, Barbosa F Jr, Bernardi R, Rhoden CR, Saldiva PH, et al. Pre and post-natal exposure to ambient level of air pollution impairs memory of rats: the role of oxidative stress. Inhal Toxicol. 2010; 22(11):910–8. DOI: 10.3109/08958378.2010.494313 [PubMed: 20569119]
61. Costa LG, Cole TB, Coburn J, Chang YC, Dao K, Roque P. Neurotoxicants are in the air: convergence of human, animal, and in vitro studies on the effects of air pollution on the brain. Biomed Res Int. 2014; 2014:736385.doi: 10.1155/2014/736385 [PubMed: 24524086]
62. Karadottir R, Attwell D. Neurotransmitter receptors in the life and death of oligodendrocytes. Neuroscience. 2007; 145(4):1426–38. DOI: 10.1016/j.neuroscience.2006.08.070 [PubMed: 17049173]
63. Volpe JJ, Kinney HC, Jensen FE, Rosenberg PA. The developing oligodendrocyte: key cellular target in brain injury in the premature infant. Int J Dev Neurosci. 2011; 29(4):423–40. DOI: 10.1016/j.ijdevneu.2011.02.012 [PubMed: 21382469]
64. Biber K, Neumann H, Inoue K, Boddeke HW. Neuronal 'On' and 'Off' signals control microglia. Trends Neurosci. 2007; 30(11):596–602. DOI: 10.1016/j.tins.2007.08.007 [PubMed: 17950926]

65. Kaur C, Ling EA. Periventricular white matter damage in the hypoxic neonatal brain: role of microglial cells. Prog Neurobiol. 2009; 87(4):264–80. DOI: 10.1016/j.pneurobio.2009.01.003 [PubMed: 19428957]

66. Matute C, Alberdi E, Domercq M, Sanchez-Gomez MV, Perez-Samartin A, Rodriguez-Antiguedad A, et al. Excitotoxic damage to white matter. J Anat. 2007; 210(6):693–702. DOI: 10.1111/j.1469-7580.2007.00733.x [PubMed: 17504270]

67. Schmitz T, Krabbe G, Weikert G, Scheuer T, Matheus F, Wang Y, et al. Minocycline protects the immature white matter against hyperoxia. Exp Neurol. 2014; 254:153–65. DOI: 10.1016/j.expneurol.2014.01.017 [PubMed: 24491957]

68. Schwarz JM, Bilbo SD. Sex, glia, and development: interactions in health and disease. Horm Behav. 2012; 62(3):243–53. DOI: 10.1016/j.yhbeh.2012.02.018 [PubMed: 22387107]

69. Tay TL, Savage J, Hui CW, Bisht K, Tremblay ME. Microglia across the lifespan: from origin to function in brain development, plasticity and cognition. J Physiol. 2016; doi: 10.1113/JP272134

70. Skaper SD, Facci L, Giusti P. Neuroinflammation, microglia and mast cells in the pathophysiology of neurocognitive disorders: a review. CNS Neurol Disord Drug Targets. 2014; 13(10):1654–66. [PubMed: 25470401]

71. Voytek B, Knight RT. Dynamic network communication as a unifying neural basis for cognition, development, aging, and disease. Biol Psychiatry. 2015; 77(12):1089–97. DOI: 10.1016/j.biopsych.2015.04.016 [PubMed: 26005114]

72. Pavlova MA, Krageloh-Mann I. Limitations on the developing preterm brain: impact of periventricular white matter lesions on brain connectivity and cognition. Brain. 2013; 136(Pt 4):998–1011. DOI: 10.1093/brain/aws334 [PubMed: 23550112]

73. 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.doi: 10.1186/1743-8977-7-12 [PubMed: 20478040]

74. 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. 2011; 119(8):1149–55. DOI: 10.1289/ehp.1002986 [PubMed: 21561831]

75. Roque PJ, Dao K, Costa LG. Microglia mediate diesel exhaust particle-induced cerebellar neuronal toxicity through neuroinflammatory mechanisms. Neurotoxicology. 2016; 56:204–14. DOI: 10.1016/j.neuro.2016.08.006 [PubMed: 27543421]

76. Allen JL, Liu X, Pelkowski S, Palmer B, Conrad K, Oberdorster G, et al. Early postnatal exposure to ultrafine particulate matter air pollution: persistent ventriculomegaly, neurochemical disruption, and glial activation preferentially in male mice. Environ Health Perspect. 2014; 122(9):939–45. DOI: 10.1289/ehp.1307984 [PubMed: 24901756]

77•. Allen JL, Oberdorster G, Morris-Schaffer K, Wong C, Klocke C, Sobolewski M, et al. Developmental neurotoxicity of inhaled ambient ultrafine particle air pollution: Parallels with neuropathological and behavioral features of autism and other neurodevelopmental disorders. Neurotoxicology. 2015; Mouse model of human third trimester equivalent exposure to ultrafine particles demonstratingneuropathological, neurochemical and behavioral consequences that parallel those seen in many human neurodevelopmental disorders. doi: 10.1016/j.neuro.2015.12.014

78. Guo L, Li B, Miao JJ, Yun Y, Li GK, Sang N. Seasonal variation in air particulate matter (PM10) exposure-induced ischemia-like injuries in the rat brain. Chem Res Toxicol. 2015; 28(3):431–9. DOI: 10.1021/tx500392n [PubMed: 25517455]

79. Cheng H, Saffari A, Sioutas C, Forman HJ, Morgan TE, Finch CE. Nano-Scale Particulate Matter from Urban Traffic Rapidly Induces Oxidative Stress and Inflammation in Olfactory Epithelium with Concomitant Effects on Brain. Environ Health Perspect. 2016; doi: 10.1289/EHP134

80. Chen JC, Wang X, Wellenius GA, Serre ML, Driscoll I, Casanova R, et al. Ambient Air Pollution and Neurotoxicity on Brain Structure: Evidence from Women's Health Initiative Memory Study. Ann Neurol. 2015; doi: 10.1002/ana.24460

81. Pujol J, Martinez-Vilavella G, Macia D, Fenoll R, Alvarez-Pedrerol M, Rivas I, et al. Traffic pollution exposure is associated with altered brain connectivity in school children. Neuroimage. 2016; 129:175–84. DOI: 10.1016/j.neuroimage.2016.01.036 [PubMed: 26825441]
82. Peterson D, Mahajan R, Crocetti D, Mejia A, Mostofsky S. Left-hemispheric microstructural abnormalities in children with high-functioning autism spectrum disorder. Autism Res. 2015; 8(1): 61–72. DOI: 10.1002/aur.1413 [PubMed: 25256103]
83. Cepeda, C., Andre, VM., Jocoy, EL., Levine, MS. NMDA and Dopamine: Diverse Mechanisms Applied to Interacting Receptor Systems. In: Van Dongen, AM., editor. Biology of the NMDA Receptor. Frontiers in Neuroscience. Boca Raton (FL): 2009.
84. Wang M, Wong AH, Liu F. Interactions between NMDA and dopamine receptors: a potential therapeutic target. Brain Res. 2012; 1476:154–63. DOI: 10.1016/j.brainres.2012.03.029 [PubMed: 22472597]
85. Win-Shwe TT, Kyi-Tha-Thu C, Moe Y, Fujitani Y, Tsukahara S, Hirano S. Exposure of BALB/c Mice to Diesel Engine Exhaust Origin Secondary Organic Aerosol (DE-SOA) during the Developmental Stages Impairs the Social Behavior in Adult Life of the Males. Front Neurosci. 2015; 9:524.doi: 10.3389/fnins.2015.00524 [PubMed: 26834549]
86. Win-Shwe TT, Fujimaki H, Fujitani Y, Hirano S. Novel object recognition ability in female mice following exposure to nanoparticle-rich diesel exhaust. Toxicol Appl Pharmacol. 2012; 262(3): 355–62. DOI: 10.1016/j.taap.2012.05.015 [PubMed: 22659509]
87. Cory-Slechta DA, Virgolini MB, Rossi-George A, Weston D, Thiruchelvam M. Experimental manipulations blunt time-induced changes in brain monoamine levels and completely reverse stress, but not Pb+/−stress-related modifications to these trajectories. Behav Brain Res. 2009; 205(1):76–87. [PubMed: 19631235]
88. Cory-Slechta DA, Merchant-Borna K, Allen J, Liu S, Weston D, Conrad K. Variations in the Nature of Behavioral Experience Can Differentially Alter the Consequences of Developmental Exposures to Lead, Prenatal Stress and the Combination. Toxicol Sci. 2013; 131:194–205. DOI: 10.1093/toxsci/kfs260 [PubMed: 22930682]
89. 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(1):38–41. DOI: 10.1016/j.neulet.2008.09.085 [PubMed: 18938223]
90. Yokota S, Moriya N, Iwata M, Umezawa M, Oshio S, Takeda K. Exposure to diesel exhaust during fetal period affects behavior and neurotransmitters in male offspring mice. J Toxicol Sci. 2013; 38(1):13–23. [PubMed: 23358136]
91. Yokota S, Oshio S, Moriya N, Takeda K. Social Isolation-Induced Territorial Aggression in Male Offspring Is Enhanced by Exposure to Diesel Exhaust during Pregnancy. PLoS One. 2016; 11(2):e0149737.doi: 10.1371/journal.pone.0149737 [PubMed: 26919122]
92. 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.doi: 10.1186/1743-8977-7-7 [PubMed: 20331848]
93. Allen JL, Liu X, Weston D, Conrad K, Oberdorster G, Cory-Slechta DA. Consequences of developmental exposure to concentrated ambient ultrafine particle air pollution combined with the adult paraquat and maneb model of the Parkinson's disease phenotype in male mice. Neurotoxicology. 2014; 41:80–8. DOI: 10.1016/j.neuro.2014.01.004 [PubMed: 24486957]
94. 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(7):1003–9. DOI: 10.1289/ehp.1002973 [PubMed: 21724521]
95. Halassa MM, Fellin T, Haydon PG. The tripartite synapse: roles for gliotransmission in health and disease. Trends Mol Med. 2007; 13(2):54–63. DOI: 10.1016/j.molmed.2006.12.005 [PubMed: 17207662]
96. Davis DA, Bortolato M, Godar SC, Sander TK, Iwata N, Pakbin P, et al. Prenatal exposure to urban air nanoparticles in mice causes altered neuronal differentiation and depression-like responses. PLoS One. 2013; 8(5):e64128.doi: 10.1371/journal.pone.0064128 [PubMed: 23734187]

97. Cheng H, Davis DA, Hasheminassab S, Sioutas C, Morgan TE, Finch CE. Urban traffic-derived nanoparticulate matter reduces neurite outgrowth via TNFalpha in vitro. J Neuroinflammation. 2016; 13:19.doi: 10.1186/s12974-016-0480-3 [PubMed: 26810976]

98. Cory-Slechta DA. Behavioral measures of neurotoxicity. Neurotoxicology. 1989; 10:271–95. [PubMed: 2616068]

99. Cory-Slechta, D., Weiss, B. Assessment of Behavioral Toxicity. In: Hayes, AW., Kruger, CL., editors. Principles and Methods of Toxicology. 6th. New York: CRC Press Taylor and Francis; 2014. p. 1831-90.

Table 1

Animal studies of cognitive deficits in response to air pollution

Study (reference number)	Species	Sample Sizes	Type of Air Pollution Exposure	Control Exposure	Outcome Measures	Results
Hougaard et al., 2008 (51)	Mice (sex not reported)	Dams=11–12 Offspring 6–10 depending upon outcome measure	Gestational exposure to diesel exhaust particles (DEP) at approximately 20 mg DEP/m3 on GDs 7–19 for one hour/day.	Filtered clean air	Learning/memory in a water maze	Significantly increased latency to find escape platform in water maze on first trial of a reversal
Yokota et al., 2015 (52)	Male mice	N=15 per treatment group	Diesel exhaust particle solutions administered subcutaneously at doses of 0 or 200 ug/kg body weight on gestational days 6, 9, 12, 15 and 18	Saline administered subcutaneously	Learning/memory in a water maze; locomotor activity, passive avoidance	No effects on locomotor activity or passive avoidance; increased latency to escape in the water maze but only significant for one day (7) of a 9 day training period; significant reduction in time spent in quadrant with hidden escape platform on probe trial
Win-Shwe et al., 2008 53)	Male mice	N=6/group	Diesel exhaust nanoparticles averaging 26 nm in size delivered 5 hr/day for 5 days per week for 4 weeks with or without concurrent administration of lipoteichoic acid, a bacterial cell wall component	Filtered (HEPA filter) clean air and clean (charcoal filter) air	Water maze	Increases in latency to escape the water maze on day 1 and 2 in responses to diesel exhaust with or without LTA; increases on day 3 only for diesel exhaust with LTA; swimming speed was not affected; no differences in visible platform test; only LTA-treated mice showed deficits in the probe trial
Win-Shwe et al., 2012 (54)	Female mice	N=6 per group	Diesel exhaust nanoparticles by inhalation at a concentration of either 35.48 ug/m^3 (moderate) or 122 ug/m^3 (high) for 5 hr/day for five days per week for 3 months	Filtered (HEPA filter) and clean (charcoal filter) air	Water maze	Increases in escape latency only for high dose that persisted across all 4 days of training, with no effects on swimming speed; no deficits in the probe trial
Win-Shwe et al., 2012 (55)	Female mice	N=8 per group	Diesel exhaust nanoparticles by inhalation at a concentration of either 47 ug/m^3 (moderate) or 129 ug/m^3 (high) for 5 hr/day for five days per week for 3 months	Filtered clean air	Novel object recognition	Significant decreases in novel object discrimination index score in the high dose diesel exhaust group

Study (reference number)	Species	Sample Sizes	Type of Air Pollution Exposure	Control Exposure	Outcome Measures	Results
Win-Shwe et al., 2014 (56)	Male mice	N=8 per group	Diesel exhaust (98 ug/$m^{3)}$ or diesel exhaust (114 ug/m^3) with secondary organic aerosols for 5 days per week for one or three months	Filtered clean air	Novel object recognition	Decreased discrimination index score in the diesel exhaust + secondary organic aerosol group, but not diesel exhaust alone
Fonken et al., 2011 (57)	Male mice	Not specified	Concentrated ambient $PM_{2.5}$ for 6 hr/day at 94 ug/m^3 for 5 days per week for 10 months	Filtered air	Barnes maze for learning and memory; olfactory abilities, forelimb grip strength, inclined screen test, rotarod, locomotor activity, forced swim test, elevated plus maze	No effects on olfaction, grip strength or motor performance; PM2.5 exposure was associated with increased latency to escape and increased error counts on the Barnes maze, but only on day 2 of a 4 day test period; Increases in escape latency were increased and correct pokes decreased in the subsequent probe trial. Increased time immobile time in forced swim test, but no differences in the elevated plus maze
Allen et al., 2014 (58)	Mice of both sexes	N=8–12 per group per sex	Concentrated ambient ultrafine particle exposure ranging from 100–20 ug/m^3 for 4 hr/day from postnatal days 4–7 and 10–13 (CAPS) with half also receiving exposure again to concentrated ambient ultrafine particles from postnatal days 56–50 (CAPS/CAPS), while the other half received filtered air (CAPS/Air)	Filtered air from postnatal days 4–7 and 10–13 with half also receiving filtered air again at postnatal days 56–60 (Air/Air) while the other half received concentrated ambient ultrafine particle exposure (Air/CAPS)	Fixed Interval schedule-controlled responding for food reward; novel object recognition ; locomotor activity	Postnatal only CAPS (CAPS/Air) significantly reduced Fixed Interval response rates and run rates in males, transient rate decreases in Air/CAPS males. Significant increases in fixed interval 60 sec response rates in Air/CAPS females, but reductions at fixed interval 120 sec in both CAPS/CAPS and Air/CAPS females. Reductions in percent change in time with the novel object, approaches to novel object in probe trial with CAPS/Air groups of both sexes; ambulatory locomotor activity significantly reduced in CAPS/CAPS females; reductions in horizontal activity in both Air/CAPS and CAPS/CAPS males
Allen et al., 2013 (59)	Male mice	N=7–8 per group	Concentrated ambient ultrafine particle exposure ranging from 96	Filtered air from postnatal days 4–7 and 10–13 with half also receiving filtered air again at postnatal days 56–	Fixed ratio waiting for reward schedule; locomotor activity	Increases in fixed ratio overall response rates and run rates and decreased

Study (reference number)	Species	Sample Sizes	Type of Air Pollution Exposure	Control Exposure	Outcome Measures	Results
			ug/m^3 for 4 hr/day from postnatal days 4–7 and 10–13 (CAPS) with half also receiving exposure again to concentrated ambient ultrafine particles from postnatal days 56–50 (CAPS/CAPS), while the other half received filtered air (CAPS/Air)	60 (Air/Air) while the other half received concentrated ambient ultrafine particle exposure (Air/CAPS)		inter-response times in CAPS/Air and CAPS/CAPS groups. Increases in the number of fixed ratio resets, reductions in CAPS/CAPS group. Comparable trends towards decreased mean waiting time with CAPS/CAPS and mean longest wait time; no effects on locomotor activity
Zanchi et al., 2010 (60)	Male rats	N=12 per group	Ambient $PM_{2.5}$ pollution from prenatal-weaning and to 150 days of age at a total monthly mass averaging 16.2 ug/m^3	Filtered air	Novel object recognition (listed as spontaneo us non-matching to sample recognition test)	Reduced discrimination index scores in males exposed from gestation to 150 days of age, but this group also exhibited less exploration during the test session