Effects of air pollution on the nervous system and its possible role in neurodevelopmental and neurodegenerative disorders

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Abstract

Recent extensive evidence indicates that air pollution, in addition to causing respiratory and cardiovascular diseases, may also negatively affect the brain and contribute to central nervous system diseases. Air pollution is comprised of ambient particulate matter (PM) of different sizes, gases, organic compounds, and metals. An important contributor to PM is represented by traffic-related air pollution, mostly ascribed to diesel exhaust (DE). Epidemiological and animal studies have shown that exposure to air pollution may be associated with multiple adverse effects on the central nervous system. In addition to a variety of behavioral abnormalities, the most prominent effects caused by air pollution are oxidative stress and neuro-inflammation, which are seen in both humans and animals, and are supported by in vitro studies. Among factors which can affect neurotoxic outcomes, age is considered most relevant. Human and animal studies suggest that air pollution may cause developmental neurotoxicity, and may contribute to the etiology of neurodevelopmental disorders, including autism spectrum disorder. In addition, air pollution exposure has been associated with increased expression of markers of neurodegenerative disease pathologies, such as alpha-synuclein or beta-amyloid, and may thus contribute to the etiopathogenesis of neurodegenerative diseases, particularly Alzheimer's disease and Parkinson's disease.

Keywords

Air pollution; Diesel exhaust; Neurotoxicity; Oxidative stress; Neuro-inflammation; Neurodevelopmental disorders; Autism; Neurodegenerative diseases; Alzheimer's disease

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1. Air pollution: sources, composition and major adverse health effects

Full recognition that poor air quality may compromise human health has been achieved only in the twentieth century. The most important episode in this regard is the so-called "London fog" in 1952. A dense smog containing sulfur dioxide and smoke particulate (from coals burning and industrial activities) descended upon London in December 1952, resulting in an unprecedented morbidity and mortality, and a final >10,000 excess deaths by February 1953 (Anderson, Thundiyil, & Stolbach, 2012; Bell & Davis, 2001; Bell, Davis, & Fletcher, 2004). Similar episodes of acute effects of air pollution of similar severity, albeit of lesser consequences, have also been reported in Belgium in 1930 and in Pennsylvania in 1948 (Bell & Davis, 2001). These episodes are believed to have prompted awareness that quality of air is an important determinant of human health, and that it needs to be considered in the overall contributions of environmental factors to potential adverse health effects. In the U.S.A., these considerations culminated in 1970 with the approval of the Clean Air Act whose main goals were the study of air pollution, and the setting of limits on emissions and on specific air pollution components. The National Ambient Air Quality Standards set limits for six primary air pollutants: carbon monoxide (CO), lead, nitrogen dioxide (NO_2), ozone (O_3), sulfur dioxide (SO_2), and particulate matter (PM). The main sources of CO are motor vehicles and industrial boilers, while NO_2 derives from motor vehicles, construction equipment, electric utilities and industrial broilers. O_3 is formed when nitrogen oxides (NO_x) react with volatile organic carbons and oxygen in the presence of heat and light. Its main sources are vehicles, factories and electric utilities. Lead is still released when garbage containing this metal is burned, while SO_2 is formed when fuel containing sulfur is burned, mostly in industrial facilities. PM is a complex mixture of acids, organic chemicals, metals and soil or dust particles (Anderson et al., 2012), which can be of natural sources or of man-made sources. The former includes volcanoes, fires, or dust storms, while the latter includes combustion in mechanical and industrial processes, tobacco smoke, and vehicle emissions (Anderson et al., 2012). PM is defined by its aerodynamic equivalent diameter, with particles with the same diameter tending to have similar settling velocity; PM_{10} is comprised of particles <10 μm in diameter, while $PM_{2.5}$ represents particles <2.5 μm in diameter. PM with a diameter between 2.5 and 10 is defined as "coarse", while PM with diameter < 2.5 is defined as "fine". Of much relevance (particularly related to neurotoxicity) is also ultrafine PM (UFPM or $PM_{0.1}$, with diameter < 100 nm). It is important to underline the fact that PM_{10} represents all particles <10 μm in diameter, and thus contains coarse, fine and ultrafine PM fractions. Ambient air pollution is continuously monitored by regulatory agencies in various countries (e.g. the Environmental Protection Agency (EPA) in the U.S.A.). However, only $PM_{2.5}$ and PM_{10} are monitored, while $PM_{0.1}$ is not. It is important to note that the current regulations are "mass-based" and thereby the contribution of UFPM to total PM may be negligible. Given the increasing evidence for UFPM neurotoxicity, including neurodevelopmental and neurodegenerative disorders (Calderon-Garciduenas, Reynoso-Robles, & Gonzalez-Maciel, 2019; Cory-Slechta et al., 2019), future regulation of $PM_{0.1}$ should consider alternatives to the mass-based approach, such as one based on the number of particles.

Furthermore, the specific composition of PM is not monitored. This latter issue may be relevant, as the assumption that $PM_{2.5}$ or PM_{10} from different sources have equivalent biological activity has received little evaluation and may not be true. Indeed, significant variations (up to two orders of magnitude) in relative composition of PM have been found (Forman & Finch, 2018) with largely different biological activities. In the E.U., air quality has been addressed by a series of directives going back to the mid-1980s. Directive 2008/50/EC on ambient air and cleaner air for Europe merges most legislation into a single directive. Air quality standards for the primary air pollutants in the U.S.A. and the E.U. are shown in Table 1.

The Air Quality Index (AQI) is a measure of air pollution, and provides information on levels of air pollutants, and in some cases on their potential adverse effects. In the U.S.A., the AQI is based on the EPA's five primary pollutants (the six indicated earlier minus lead) and ranges from 0 to 500, with increasing levels of concerns and a different coloring scheme for each level, for easy comprehension by the general population (Table 2). In many urban areas in some countries (e.g. India or China) the AQI could remain above 200 for several days and even exceed it. During the Summer of 2018, the AQI in the city of Seattle, Washington, U.S.A., normally at or below 50, increased for several days to 150–200, because of raging wildfires on the West Coast. Particularly in urban areas, traffic-related air pollution (TRAP) is a major contributor to global air pollution, and diesel exhaust (DE) is one of its most important components (Ghio, Smith, & Madden, 2012). Indeed, as global population increases, anthropogenic pollutants resulting from increased urban density and transportation demands threaten to compromise air quality as never before (Cramer, 2002). In certain megacities such as New Delhi, where use of diesel-powered vehicles predominates, it is estimated that traffic may contribute to up to 72% of air pollution (Goyal, Ghatge, Nema, & Tamhane, 2006). Despite abundant alternative energy sources, diesel remains a fuel of choice for mass transit vehicles, passenger vehicles, heavy machinery, and freight conveyances, resulting in DE being considered as a major contributor to TRAP (Verboven, 2002).

DE is a major constituent of ambient PM, particularly $PM_{2.5}$ and UFPM (USEPA, 2002), and DE exposure is often utilized as a measure of TRAP. DE contains more than forty toxic air pollutants, including nitrogen and sulfur oxides, CO, hydrocarbons, volatile organic compounds (VOCs), metals, organic and elemental carbon, and PM in a variety of sizes, with its makeup varying by engine load conditions and fuel composition (Cooney and Hickey, 2008; Lim, Lim, & Yu, 2009). In recent years, improved diesel engine technology and the use of specialized catalytic converters have changed the composition of DE, resulting in an output lower in concentration of coarse fraction particulates, nitrogen oxides, volatile organic compounds, and carbon monoxide (Su et al., 2008). Additionally, more stringent air quality guidelines in certain localities have reduced allowable sulfur content of diesel fuel, resulting in a lower output of sulfur oxides (Stanislaus, Marafi, & Rana, 2010). However, the content of $PM_{2.5}$ and of UFPM is estimated to be unchanged, and the inflammatory potential of DE particulates from these low emission engines is increased, due to the higher proportion of fine particulates (Su et al., 2008). It is precisely these fine particulates that are most concerning, as they are capable of penetrating the epithelium of the

lungs and the olfactory mucosa, where they can enter into general circulation in the body (Oberdörster et al., 2004).

Inhalation is the main route of exposure to air pollutants. The larger particles (PM_{10}) are filtered out by the nose and upper airways, while $PM_{2.5}$ are deposited primarily in the lungs, with some ingested after mucociliary transport into the throat (Forman & Finch, 2018). $PM_{2.5}$ can enter the olfactory epithelium and are transported into the olfactory bulb, further travelling to the olfactory cortex and other brain regions (Ajmani, Suh, & Pinto, 2016). A series of studies by Oberdörster et al. (Oberdörster et al., 2004; Oberdörster & Utell, 2002) has shown clearly that UFPM also enters the brain through the olfactory nerves and distribute to other regions such as the cerebral cortex and the cerebellum. Once PM reaches the lung, it can translocate to the blood. Though lung to blood translocation is not very efficient (Forman & Finch, 2018), some PM can also reach the brain, and certainly other organs, via this pathway. A study by Maher et al. (2016) showed that magnetite nanoparticles abundant in PM pollution were present in brain from individuals from the Mexico City Metropolitan area, even at a young age.

Air pollution is considered "one of the great killers of our age", as it was responsible in 2015 for 6.4 million deaths worldwide, of which 2.8 million were from household air pollution and 4.2 million from ambient air pollution (Landrigan, 2017). In the same year, air pollution was responsible for 19% of cardiovascular deaths worldwide, 21% of stroke deaths, and 23% of lung cancer deaths (Landrigan, 2017). While household air pollution has been declining since the 1990s, due to the changing of heating and cooking fuels (e.g. from wood or dung to gas or electricity), this has been offset by increases in ambient air pollution with deaths increasing mostly in rapidly industrializing countries.

The first and most studied target for air pollution toxicity are the air-ways. Symptoms such as nose and throat irritation, bronchoconstriction and dyspnea are common in individuals with pre-existing respiratory conditions upon acute exposure to high levels of air pollution as well as chronic exposures. These symptoms are believed to be primarily due to SO_2 and NOx (Kampa & Castanas, 2008). PM that penetrates the alveolar epithelium and ozone are responsible for lung inflammation. PM and some metals may induce emphysema and cause lung cancer (Pope & Dockery, 2006). In the case of DE exposure, a potential increase in lung tumors has also been suggested (Benbrahim-Tallaa et al., 2012). In addition to the respiratory system, the cardiovascular system has emerged in the past two decades as an important target for air pollution toxicity (Brook et al., 2010; Brook & Rajagopalan, 2007). Systemic inflammatory changes caused by air pollution affect blood coagulation, atherosclerosis progression, and are associated with consistent increased risk for cardiovascular events (Brook et al., 2010; Brook & Rajagopalan, 2007; Pope & Dockery, 2006). Other systems (e.g. urinary, digestive, etc.) can also be affected by exposure to high levels of air pollution (Kampa & Castanas, 2008), with increasing evidence indicating the Central Nervous System (CNS) as a primary important target.

2.   The central nervous system as a target for air pollution

Inhaled UFPM may enter the CNS either by way of the olfactory nerve, or through the tight endothelial junctions that comprise the vascular interface of the blood-brain barrier, which may be rendered more permeable by higher levels of peripheral oxidative stress and inflammation (Lochhead et al., 2010). Increased peripheral inflammation and macrophage activation may also exacerbate existing neuroinflammation, as these conditions can result in increased permeability of the blood-brain barrier to allow both the migration of activated macrophages and the passive diffusion of pathogens and other foreign bodies into the CNS (Elwood, Lim, Naveed, & Galea, 2017; Lochhead et al., 2010).

In recent years evidence from human epidemiological and animal studies supports that air pollution may negatively affect the CNS and contribute to CNS diseases (Calderon-Garciduenas et al., 2002; Block & Calderon-Garciduenas, 2009; Genc, Zadeoglulari, Fuss, & Genc, 2012; Block et al., 2012; Costa et al., 2014; Costa et al., 2017a; Sram, Veleminsky, Veleminsky, & Stejskalova, 2017; Russ, Reis, & van Tongeren, 2019). $PM_{2.5}$ and UFPM are of particular concern, as these particles can enter systemic circulation and distribute to the brain and other organs (Genc et al., 2012; Oberdörster et al., 2004; Oberdörster & Utell, 2002), as well as gain direct access to the brain through the nasal olfactory mucosa (Garcia, Schroeter, & Kimbell, 2015; Lucchini, Dorman, Elder, & Veronesi, 2012; Oberdörster et al., 2004; Peters et al., 2006). Decreased cognitive function, olfactory dysfunction, auditory deficits, depressive symptoms and other adverse neuropsychological effects have been reported in humans (Calderon-Garciduenas et al., 2011, 2010; Fonken et al., 2011; Freireet al., 2010; Guxens & Sunyer, 2012; Lee et al., 2019; Petkus et al., 2019; Ranft, Schikowski, Sugiri, Krutmann, & Kramer, 2009). Controlled acute exposure to DE (300 μg/m^3) has been shown to induce EEG changes (Crüts et al., 2008). In highly exposed individuals, post-mortem investigations have revealed increased markers of oxidative stress and neuroinflammation (Calderon-Garciduenas et al., 2008; Calderon-Garciduenas et al., 2011; Calderon-Garciduenas et al., 2012; Levesque et al., 2011b).

Animal studies corroborate the human observations (Costa et al.,2014). For example, dogs exposed to heavy air pollution in Mexico City presented evidence of chronic inflammation and neurodegeneration in various brain regions (Calderon-Garciduenas et al., 2002, 2003), and mice exposed to traffic in a highway tunnel had higher levels of pro-inflammatory cytokines in the brain (Bos et al., 2012). Exposure of rats to $PM_{1.0}$ (16.3 μg/m^3, with particle number of 11,257/m^3) for 3 to 6 months, caused microglia activation in the hippocampus (Bai et al., 2019). Controlled exposure to DE has been reported to alter motor activity, spatial learning and memory, novel object recognition ability, and emotional behavior, as well as to cause oxidative stress and neuro-inflammation in the CNS (MohanKumar, Campbell, Block, & Veronesi, 2008; Gerlofs-Nijland et al., 2010; Win-Shwe & Fujimaki, 2011; Levesque, Taetzsch, et al., 2011b; Ehsanifar et al., 2019). Changes in the expression of genes related to antioxidant defenses and to inflammation have been reported in the brain of rats exposed to biodiesel fuels for 7 or 28 days (Valand et al., 2018). A three-week exposure to DE (250 μg/m^3, 6 h/day, 5 day/week) was found to increase lipid peroxidation and expression of pro-inflammatory cytokines in different mouse brain regions (Dao et al., unpublished data). Even an acute exposure to DE (250 μg/m^3 for 6 h) has been shown to

cause microglia activation, oxidative stress, neuroinflammation, and to impair adult neurogenesis (Coburn, Cole, Dao, & Costa, 2018; Cole et al., 2016). In most cases the effects were more pronounced in males than in females (Cole et al., 2016; Roqué, Dao, & Costa, 2016; Coburn et al., 2018), a finding that may be related, among others, to sex differences in microglia (Schwartz & Bilbo, 2012), or to the differential expression of antioxidant and anti-inflammatory genes (Giordano et al., 2013; Torres-Rojas & Jones, 2018).

Evidence that air pollution affects the CNS, in addition to its more studied peripheral targets, is undeniable, and supported by dozens of human and animal studies. Of much interest is whether air pollution may be causally associated with neurological or neuropsychiatric disorders, particularly neurodevelopmental and neurodegenerative diseases, and this is discussed in the following sections, together with consideration on possible underlying mechanisms.

3. Developmental neurotoxicity of air pollution and its possible role in neurodevelopmental disorders

Epidemiological and animal studies suggest that young individuals may be particularly susceptible to air pollution-induced neurotoxicity (Calderon-Garciduenas et al., 2008; Calderon-Garciduenas et al., 2011; Calderon-Garciduenas et al., 2012; Freire et al., 2010; Guxens et al., 2014; Guxens & Sunyer, 2012). Studies in Mexico City have revealed elevated levels of neuroinflammatory markers in the brain of children exposed to high air pollution, as well as cognitive deficits (Calderon-Garciduenas et al., 2008; Calderon-Garciduenas et al., 2013, 2011). Newman et al. (2013) reported hyperactivity in 7-year old children associated with early life exposure to traffic-related air pollution. A retrospective cohort study in Catalonia, Spain, also found an association between air pollution (assessed as living <300 m from a motorway) and incidence of attention deficit hyperactivity disorder (ADHD) (Saez, Barcelo, Farrerons, & Lopez-Casasnovas, 2018). In contrast, a large study with eight European population-based birth/child cohorts reported no association between air pollution exposure and ADHD (Forns et al., 2018), and negative findings were also reported in a study in Sweden (Oudin et al., 2019). A recent systematic review concluded that the association between air pollution and ADHD is weak, and that further high-quality studies are needed to clarify this association (Donzelli, Llopis-Gonzalez, Llopis-Morales, Cioni, & Morales-Suarez-Varela, 2020). In six European cohorts, exposure to air pollution during pregnancy was found to be associated with delayed psychomotor development (Guxens et al., 2014). A recent study reported that exposure to traffic-related air pollution is inversely associated with sustained attention in adolescents (Kicinski et al., 2015) and was shown to lower cognitive development in primary school children (Sunyer et al., 2015). The BREATHE project in Catalonia, Spain, found that exposure to TRAP was associated with behavioral problems in children, including cognitive development (Forns et al., 2017, 2016), and that the *APOEε4* genotype represented a risk factor for some of them (Alemany et al., 2018). Another recent study in the U.K. reported that children with intellectual disabilities were found to be significantly more likely to live in areas with high levels of DE-PM, NO_2 and CO (Emerson, Robertson, Hatton, & Baines, 2018).

Experimental studies support the hypothesis that air pollution may be a developmental neurotoxicant. Ema, Naya, Horimoto, and Kato (2013) indicated that developmental exposure to DE may cause toxicity and neurotoxicity. In utero exposure to high levels of DE (1.0 mg/m^3) caused alterations in motor activity, motor coordination and impulsive behavior in male mice (Suzuki et al., 2010; Yokota et al., 2009, 2013). Early postnatal exposure of mice to concentrated ambient PM was reported to cause behavioral changes (enhanced bias towards immediate rewards), as well as long-term impairment of short-term memory and impulsivity-like behavior (Allen et al., 2013; 2014a). Additional studies in mice showed that post-natal administration (PND4–7 and 10–13, for 4 h/day) of DE-PM (∼100 μg/m^3) caused changes in GFAP expression in various brain regions (Morris-Schaffer et al., 2019), while a lower exposure UFPM (∼45 μg/m^3) caused male-specific learning and memory dysfunctions (Cory-Slechta, Allen, Conrad, Marvin, & Sobolewski, 2018). Depression-like responses were found in mice exposed prenatally to urban air nanoparticles (Davis et al., 2013). Additional studies have shown that developmental DE exposure of mice alters motor activity, spatial learning and memory, and novel object recognition ability, and causes changes in gene expression, neuroinflammation, and oxidative damage (Hougaard et al., 2008; Hougaard, Saber, Jensen, Vogel, & Wallin, 2009; Tsukue, Watanabe, Kumamoto, Takano, & Takeda, 2009; Win-Shwe, Yamamoto, Fujitani, Hirano, & Fujimaki, 2008; Win-Shwe et al., 2014). In another study, rats were exposed to PM$_{0.2}$ (340 μg/m^3) during gestation and until 25 weeks of age; male rats exhibited activated microglia, impaired hippocampal neurogenesis, and alteration of the blood-brain-barrier, together with behavioral symptoms of depression and deficits in contextual memory (Woodward et al., 2018). In rabbits, Bernal-Melendez et al. (2019) found that prenatal exposure to DE (1 mg/m^3) from gestational day 3 to 27, caused changes in olfactory bulb morphology and in olfactory-based behaviors in the offspring, together with alterations in monoaminergic neurotransmission.

Altogether, findings in human and in multiple animal models indicate that exposure to air pollution may damage the developing brain and potentially contribute to neurodevelopmental disorders. A major neurodevelopmental disorder is autism spectrum disorder (ASD), and evidence from human epidemiological and from controlled animal studies suggests that air pollution may be associated with its etiology. The following sections will thus focus on ASD and on the possible contribution of air pollution to this disorder.

3.1. Autism spectrum disorder

Autism is a neurodevelopmental disorder characterized by marked reduction of social and communicative skills, and by the presence of stereotyped behaviors (Levy, Mandell, & Schultz, 2009; Sharma, Gonda, & Tarazi, 2018). The term ASD is usually utilized to include autism and a range of similar disorders. The symptoms of ASD are present before the age of three, and are often accompanied by abnormalities of cognitive functioning, learning, attention, and sensory processing (Levy et al., 2009). The incidence of ASD seems to have increased in the past few decades, and it is now estimated at about 1 in 36 children, up from 1 in 150 children in 2000 (Boyle et al., 2011; Wingate et al., 2012; Sharma et al., 2018; Xuet al., 2018). While this prevalence is similar across ethnic and socioeconomic background, a significant sex difference exists, with a prevalence 4–5 times higher in boys than in girls

(Schaafsma & Pfaff, 2014; Sharma et al., 2018; Xu et al., 2018). The economic burden of caring for an individual with ASD and the associated intellectual disability during his or her lifespan has been estimated at $2.4 million (Buescher, Cidav, Knapp, & Mandell, 2014). The etiological basis of ASD is unknown, and susceptibility is attributable to both genetic and environmental factors (Gaugler et al., 2014; Hallmayer et al., 2011; Kalkbrenner, Schmidt, & Penlesky, 2014; Landrigan, 2010; Levy et al., 2009; Lyall, Schmidt, & Hertz-Picciotto, 2014; Rossignol, Genuis, & Frye, 2014). Candidate susceptibility genes for ASD have been identified, but no single anomaly appears to predominate, with the total fraction of ASD attributable to genetic inheritance expected to approach only about 30–50% (Gaugler et al., 2014; Sandin et al., 2014). Studies of ASD concordance in monozygotic and dizygotic twins suggest a moderate genetic heritability and a substantial environmental component (Hallmayer et al., 2011). Thus, ASD likely results from the complex interactions among multiple genes conferring vulnerability and diverse environmental factors (Hertz-Picciotto, Schmidt, & Krakowiak, 2018). Among environmental chemicals and drugs potentially associated with ASD, in addition to air pollution (discussed below), the following have been reported: pesticides (organophosphates, pyrethroids), phthalates, polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs), and CNS drugs (valproic acid, antidepressants) (Hertz-Picciotto et al., 2018; Sharma et al., 2018). Of much interest are the findings of an association between maternal infection and ASD (Minakova & Warner, 2018; Patterson, 2011). Studies in various animal species have demonstrated that maternal immune activation (MIA) increases neuroinflammation in the placenta and in the fetal brain, leading to offspring which display ASD-like behaviors (Bauman et al., 2014; Malkova, Yu, Hsiao, Moore, & Patterson, 2012).

Children with ASD present various morphological abnormalities in the brain (Gilbert & Man, 2017; Kulesza, Lukose, & Stevens, 2011; Levy et al., 2009; Stoner et al., 2014; Wegiel et al., 2010), and alterations in certain neurotransmitter systems (e.g. GABA, glutamate, serotonin) (Lam, Aman, & Arnold, 2006; Coghlan et al., 2012; Yang et al. 2014). There is a strong association between decreased reelin, a glycoprotein which modulates neuronal migration in the developing CNS, and ASD (Fatemi et al., 2005; Folsom & Fatemi, 2013). DNA methylation is also altered in the autistic brain, suggesting that epigenetic dysregulation may contribute to ASD (Berko & Greally, 2015; Nardone et al., 2014). Increasing evidence indicates that children with ASD have higher levels of oxidative stress (Frustaci et al., 2012; Napoli, Wong, & Giulivi, 2013; Rose et al., 2012), as well as microglia activation, neuroinflammation and increased systemic inflammation (Chez, Dowling, Patel, Khanna, & Kominsky, 2007; Morgan et al., 2010; Ashwood et al., 2011; El-Ansary & Al-Ayadhi, 2012; Tetreault et al., 2012; Theoharides, Asadi, & Patel, 2013; Suzuki et al., 2013; Depino, 2013).

3.2. Air pollution and autism spectrum disorder

Several epidemiological studies have found associations between exposures to TRAP and ASD (Costa, Cole, et al., 2017a). Two studies in California by Volk, Hertz-Picciotto, Delwiche, Lurmann, and McConnell (2011); Volk, Lurmann, Penfold, Hertz-Picciotto, and McConnell (2013) found that residential proximity to freeways and gestational and early-life exposure to traffic-related air pollution were associated with ASD (OR = 1.86; 95% CI =

1.04–3.45). Similar results were obtained in another epidemiological study in California (Becerra, Wilhelm, Olsen, Cockburn, & Ritz, 2013). Furthermore, another study pulling from the Nurses' Health Study II, found that perinatal exposure to DE was significantly associated with ASD, particularly in boys (Roberts et al., 2013). A similar boy-specific association between $PM_{2.5}$ exposure and ASD was reported in a large Southern California pregnancy cohort (Jo et al., 2019). Two studies in Taiwan and in Pennsylvania also reported an increased risk of ASD associated with PM (Jung, Lin, & Hwang, 2013; Talbott et al., 2015). Additionally, a study in two cohorts in North Carolina and California reported an association between PM exposure and ASD, particularly when exposure occurred in the third trimester of pregnancy (Kalkbrenner et al., 2015). The higher susceptibility of third trimester exposure was also evidenced by a study of Raz et al. (2015) in the Nurses' Health Study II cohort. A population-based cohort study in Vancouver (British Columbia, Canada) reported an association between exposure to NO (10 ppb) and ASD but not for NO_2 (10 ppb) or $PM_{2.5}$ (10 μg/m^3) (Pagalan et al., 2019), and an association between O_3 (~40 ppb) and $PM_{2.5}$ (~15 μg/m^3) exposure and ASD was found in another study in metropolitan Cincinnati, Ohio (Kaufman et al., 2019). In a Swedish cohort, Oudin et al. (2019) found an association between maternal exposure to NO_x (mean 17.7 μg/m^3, range 3.5–48.6 μg/m^3) and ASD. In Shanghai, China, Chen et al. (2019) found that exposure to PM_1 (49 μg/m^3), $PM_{2.5}$ (66 μg/m^3), and PM_{10} (95 μg/m^3) during the first three years of life significantly increased the risk of ASD. A recent multisite case-control study reported a significant association between ASD and $PM_{2.5}$ exposure during the first year of life (OR = 1.3; 95% CI = 1.0–1.6) and between ASD and O_3 during the third trimester (OR=1.2; 95% CI 1.1–1.4) (McGuinn et al., 2020). Though these cohort and case-control studies show moderate to strong associations between exposure to air pollution in utero and/or early in life and risk of ASD, some have significant limitations due to the exposure matrix and multiple confounding factors (Fordyce, Leonhard, & Chang, 2018). A recent systematic review and meta-analysis concluded that there is evidence for an association between maternal exposure to PM**2.5** and ASD, only weak evidence for NO_2 exposure, and little evidence for PM_{10} or O_3 exposure (Chun, Leung, & McDonald, 2020). A recent study in Tehran, Iran, has reported a lack of association between air pollution and ASD (Yousefian et al., 2018); however, only PM_{10}, SO_2 and various solvents were measured in air.

Notwithstanding the limitations of human epidemiological studies, animal studies in general agree with the positive human observations (Costa et al., 2014; Costa, Chang, & Cole, 2017b; Costa, Chang, & Cole, 2017b). Prenatal and early life exposure of mice to DE is associated with behaviors like those present in humans with ASD. These include higher levels of motor activity, elevated levels of self-grooming, and increased rearing (Thirtamara Rajamani et al., 2013). Postnatal exposure to concentrated ambient ultrafine particles [on postnatal day (PND) 4–7 and 10–13] caused persistent glial cell activation (both microglia and astrocytes), and ventriculomegaly (lateral ventricular dilation), which occurred preferentially in male mice (Allen et al., 2014b; Allen et al., 2014a). Changes in cytokines and neurotransmitters, which were brain region- and sex-specific were also found in these latter studies (Allen, Liu, Weston, et al., 2014a). These investigators also reported a decreased corpus callosum in both male and female mice, and an increase of glutamate levels, with an excitatory/inhibitory imbalance, all relevant to ASD (Allen et al., 2017). In

addition, they also reported male-specific alterations in social novelty preferences (an indication of low sociability) and a reduction in testosterone levels (Sobolewski et al., 2018). Tachibana et al. (2015) found that prenatal exposure to DE disrupts DNA methylation in the brain. Prenatal exposure to UFPM (mean 93 μg/m^3; range 33–184 μg/m^3) from gestational day (GD) 0.5 to GD16.5 caused a hypermyelination of the cerebellum in male mice only, accompanied by ultrastructural abnormalities and an increase in iron content (Klocke et al., 2018). These effects are also seen in ASD (Fatemi et al., 2012).

Chang, Cole, and Costa (2018) found that perinatal exposure of mice to DE at environmentally relevant concentrations (250–300 μg/m^3, from GD 0 to PND 21) caused significant behavioral deficits in the domains of persistent/repetitive behaviors (T-maze and marble burial tests), communication (isolation-induced ultrasonic vocalization and responses to social odors), and social interactions (reciprocal interaction and social novelty tests). Interestingly, the effects of developmental DE exposure were more robust if exposure occurred in both the pre-natal (GD 0 - birth) and post-natal (PND 1–21) periods, in agreement with observations in humans. Indeed, considering the differences in relative rate of brain development between mice and humans, studies indicated that the association between air pollution and ASD is stronger when exposure occurs in the third trimester of pregnancy or early postnatally (Chen et al., 2019; Kalkbrenner et al., 2015; Raz et al., 2015; Rich et al., 2015; Schembari et al., 2015). In a follow-up study, Chang, Daza, Hevner, Costa, and Cole (2019) reported neuroinflammation [increase in interleukin-6 (IL-6)] and reduced expression of reelin in the cerebral cortex of DE-exposed mice, together with subtle alterations in cortical layering of the somatosensory cortex, as also found in ASD (Stoner et al., 2014). In summary, there is suggestive evidence from human epidemiological studies that in-utero and early-life exposure to air pollution and to TRAP is associated with an increased risk of ASD. Controlled animal studies also indicate that developmental exposure to TRAP induces behavioral, biochemical, and morphological effects that are also seen in ASD.

4. Air pollution and neurodegenerative disorders

Aging is associated with a wide variety of clinical and pathological conditions which can be classified generally as neurodegenerative diseases. There is evidence that the aging brain may be particularly susceptible to air pollution-induced neurotoxicity, as epidemiological studies have identified significant behavioral effects, particularly cognitive effects, associated with high air pollution exposure in the elderly (Chen et al., 2015; Power et al., 2011; Ranft et al., 2009; Weuve et al., 2012). Examples of neurodegenerative diseases are Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD), with AD and other dementias being the most common, followed by PD (Musgrove, Jewell, & Di Monte, 2015). The main risk factor for neurodegenerative diseases is indeed represented by aging. In the U.S.A., the number of individuals with AD dementia is expected to increase from the current 5 million to about 14 million in 2050 due to the aging of the population (Hebert, Weuve, Scherr, & Evans, 2013). Similarly, in the E.U. it is estimated that by 2060 one third of the population will be aged 65+, and the number of people with various dementias, currently around 10 million, is expected to double (Maresova, Klimova, Novotny, & Kuca, 2016). Most neurodegenerative

diseases have complex clinical and pathological pictures, and for most, their etiology is unknown (Musgrove et al., 2015). In some cases, relevant susceptibility genes have been identified, but environmental factors or gene-environment interactions are believed to play a very important role in most cases. The following sections discuss the association of air pollution exposure with AD and PD in more detail, as these neurodegenerative diseases represent the most common ones, and those for which most evidence is available of a potential relationship with air pollution (Costa, 2017).

4.1. Alzheimer's disease

AD is the main type of dementia present in individuals over 65, accounting for nearly two thirds of all dementia cases (Prince et al., 2013), and is one of the great health care challenges of the 21st century (Scheltens et al., 2016). AD is the prototypical dementia, with disturbances starting in the domain of episodic memory, followed by deficits in language, attention, and executive functions. The number of cases in the world is predicted to reach 115 million by 2050. Other common types of dementia include vascular dementia, whose causes are found in cardiovascular pathology and which presents with clinical signs involving deficits in attention, information processing, and executive function (O'Brien & Thomas, 2015), as well as dementia with Lewy bodies, with clinical signs including hallucinations, Parkinsonism, and altered cognitive status (Walker, Possin, Boeve, & Aarsland, 2015). The brain of AD patients presents diffuse cortical and hippocampal atrophy, and accumulation of abnormally folded amyloid beta (Aβ) and of tau proteins in amyloid plaques and neuronal tangles, which are the neuropathological hallmarks of AD (Khan & Bloom, 2016; Selkoe & Hardy,2016). Amyloid precursor protein (APP) is cleaved by secretases to generate an Aβ polypeptide Aβ42 or Aβ40 with the former being the major form found in amyloid plaques (Pressman & Rabinovici, 2014). Neurofibrillary tangles are composed of hyperphosphorylated tau protein, which cause disassembly of microtubules. Rare mutations in a few genes such as APP, PSEN1 and PSEN2 (presenilins, which provide the catalytic subunit to the secretase which cleaves APP) confer a high risk for AD (Scheltens et al., 2016). However, the major genetic risk factor for AD is apolipoprotein E (APOE); of its three isoforms, APOEε4 predisposes the carrier to AD (Riedel, Thompson, & Brinton, 2016). Indeed, the prevalence of APOEε4 carriers in AD cases is about 60%, while APOEε4 homozygotes are about 10–15%, particularly in Northern Europe (Ward et al., 2012).

4.2. Air pollution and cognitive decline

In the past few years, various epidemiological studies have investigated the possible contribution of air pollution to AD (Cipriani, Danti, & Borin, 2018; Killin, Starr, Shiue, & Russ, 2016; Paul, Haan, Mayeda, & Ritz, 2019; Power, Adar, Yanosky, & Weuve, 2016). Several studies have focused on various assessments of cognitive impairment, as this is an initial important aspect of AD (Clifford, Lang, Chen, Anstey, & Seaton, 2016; Cohen & Gerber, 2017; Peters, Peters, Booth, & Mudway, 2014). Many of these studies have been carried out in the elderly (>65 years), and with few exceptions, have found that increasing levels of air pollution, particularly TRAP, was associated with diminished cognitive abilities (Costa, 2017). For example, Ranft et al. (2009) reported that in women over 65 years old, exposure to $PM_{2.5}$ and PM_{10} was associated with increased mild cognitive impairment

(MCI). Power et al. (2011) found a strong association between TRAP and decreased cognitive function in older men; additionally, residing near major roadways was associated with poor performance in a series of cognitive tests in a New England population of over 65 years (Wellenius et al., 2012). Higher levels of PM**2.5** were associated with faster cognitive decline in the Nurses' Health Study Cognitive Cohort, which included almost 20,000 women aged 70 to 81 years (Weuve et al., 2012). In two separate studies, Ailshire and Crimmins (2014) and Ailshire and Clarke (2015) reported that PM**2.5** was associated with decreased cognitive function in adults 50 years or older. Similar findings were reported for populations in the U.K. (Tonne, Elbaz, Beevers, & Singh-Manoux, 2014), Los Angeles (Gatto et al., 2014), Germany (Tzivian et al., 2016), and China (Zeng, Gu, Purser, Hoenig, & Christakis, 2010). A recent study in older (> 75 years) U.S. women found an increased risk of cognitive decline and of dementia with increasing exposure to $PM_{2.5}$ (Cacciottolo et al., 2017). A study in a population of Puerto Rican adults (age 45–75 years) in the Greater Boston area, showed an association between long-term exposure to black carbon and nickel (tracers of traffic and oil combustion, respectively), and a decrease in cognitive function (Wurth et al., 2018). Thus, positive association between TRAP and MCI were found in multiple studies in different parts of the world, though two negative studies, both in the U.S. (Loop et al., 2013; Wilker et al., 2016,) found no association with memory impairment. Overall, the evidence to date is sufficiently consistent in indicating that exposure to air pollution is associated with cognitive decline in the elderly. Unfortunately, controlled animal studies in this area are still limited, and epidemiological studies present some limitations (e.g. endpoint measured, different indices of air pollution), as recently underlined (Clifford et al., 2016; Peters et al., 2015).

4.3. Air pollution and Alzheimer's disease

Several other epidemiological studies have focused on the specific association between air pollution and AD and other dementias, rather than only cognitive impairment (Kilian & Kitazawa, 2018; Shou, Huang, Zhu, Liu, & Hu, Y 7 Wang, H., 2019). In Taiwan, three studies have reported associations between air pollution and AD. Chang et al. (2014) found an increased risk of AD with increasing NO_2 and CO. Jung, Lin, and Hwang (2015) reported a significant risk for AD associated with O_3 and $PM_{2.5}$. A third case-control study by Wu et al. (2015) found that high PM_{10} or O_3 exposures were associated with AD and vascular dementia (OR = 4.17 and 2.00, respectively). In Germany, exposure of older women to PM**2.5** and to NO_x was associated with increased risk of AD (Schikowski et al., 2015), and in Sweden, Oudin et al. (2016) reported that TRAP was a risk factor for AD and vascular dementia, a finding later confirmed in the same population, with estimates of NO_x exposure of ~26 µg/m^3 (Andersson, Oudin, Sundstrom, Forsberg, & Adolfsson, 2018). In addition, a large population-based cohort study in Canada (involving about 2.2 million individuals aged 55–85 years), found an HR for dementia for people living less than 50 m (164 ft) from a major traffic road of 1.07–1.12, suggesting that 7–11% of dementia cases in patients who live near major roads is attributable to traffic exposure (Chen et al., 2017). $PM_{2.5}$ and NO_2 were positively associated with dementia, but a contribution from other factors, particularly noise, could not be ruled out (Chen et al., 2017). Using a different approach, Zanobetti, Dominici, Wang, and Schwartz (2014) and Kioumourtzoglou et al. (2016) in the U.S. examined the rate of hospitalization for AD and short- or long-term exposure to PM**2.5**,

exposure to which was associated with a significant increase in hospitalization for AD in both studies. Two studies in the E.U. examined occupational exposure to DE and risk of AD and dementia; Helou and Jaecker (2014) found that occupational exposure to DE and to other fuels and certain petroleum-based solvents was associated with an increased risk of AD and of mixed-type dementia among French workers, while Koeman et al. (2015) reported no associations between occupational exposure to DE and solvents and non-vascular dementia in Dutch workers.

In a limited number of cases, it has been possible to examine the brains of individuals exposed to air pollution, and these findings are useful to design and compare with animal studies. In autopsy samples from children, young adults or middle-aged individuals from the highly polluted Mexico City metropolitan area, several studies by Calderon-Garciduenas found increased markers for AD in various brain regions. In an initial study (Calderon-Garciduenas et al., 2004), increased Aβ42 levels were found in frontal cortex and hippocampus of individuals exposed to air pollution, together with increased levels of cyclooxygenase-2 (COX2), an indicator of neuroinflammation which is induced by pro-inflammatory cytokines and is increased in AD. In a follow-up study, similar findings were also reported in olfactory bulb and frontal cortex of young adults from Mexico City; Aβ42 was detected in 58% of young individuals and in 80% of adults (Calderon-Garciduenas et al., 2008). A particularly jarring study in a group of children and young adults (average age = 13 years), found that 51% had Aβ diffuse plaques compared to 0% in controls, and 40% exhibited tau hyperphosphorylation (Calderon-Garciduenas et al., 2012). In agreement with these findings, levels of Aβ42 were significantly decreased in cerebrospinal fluid (CSF) from highly exposed Mexico City children (Calderon-Garciduenas et al., 2016a). This is alarming, as decreases in CSF Aβ42 are considered a very early change in AD, which precede aggregation and deposition of Aβ42 in plaques and may occur decades before the onset of symptoms (Blennow et al., 2015). More recently, Calderon-Garciduenas et al., 2018b) reported higher levels of non-phosphorylated tau (a marker of axonal damage and of AD axonal pathology) in the CSF of 507 children and young adults (age 12.8 ± 6.7) exposed to high air pollution in Mexico City. In the same highly polluted metropolitan Mexico City area, significant increases of hyperphosphorylated tau and of amyloid plaques were found in the olfactory bulb of infants, children, teens and adults under 40 years (Calderon-Garciduenas et al., 2018a). In addition to these studies on early-life exposure and AD, a recent study in older females concluded that late-life exposure to PM**2.5** was associated with an accelerated decline in episodic memory, affecting immediate recall and new learning, and was paralleled by an increased incidence of AD pattern similarity, as assessed by MRI (Younan et al., 2020).

The limited biochemical evidence available from post-mortem human brains or from CSF appear to be supported by similar findings deriving from animal studies. High levels of expression of COX2 and of Aβ42 were found in brains of dogs exposed to air pollution in Mexico City (Calderon-Garciduenas et al., 2003). Controlled experimental studies showed that exposure of male rats to DE (311 or 992 μg/m^3 for six months) increased levels of Aβ42 and of phosphorylated tau (pS199) in cerebral cortex (Levesque, Taetzsch, et al., 2011b). Mice exposed for a short period (3 h) to nickel nanoparticles (as a model of air pollution)

had a significant increase of brain Aβ40 and Aβ42 levels (Kim et al., 2012), while rats exposed to DE nanoparticles (0.3–1.0 mg/L) for three months had higher levels of COX2 and of Aβ42 in various brain regions (Durga, Devasena, & Rajasekar, 2015). In mice exposed to a relatively low level of $PM_{2.5}$ (66 μg/m^3) for 9 months there was an increase in Aβ40, BACE (beta-site APP-cleaving enzyme), and COX2, as well as a decrease of APP, while phosphorylated tau was unchanged (Bhatt, Puig, Gorr, Wold, & Combs, 2015). Similar findings were also reported in vitro in immortalized mouse neurons; exposure to DE particles (50 μg/ml) caused a significant increase in levels of APP and BACE (Milani et al., 2018). Exposure to nanoparticles by inhalation for 15 weeks caused an increase in Aβ42 in brain of mice (Cacciottolo et al., 2017). In the cerebral cortex of male mice exposed for 10 weeks to DE (250 μg/m^3, 6 h/day, 5 days/week), Coburn et al. (unpublished) found increases in the levels of Aβ42, phosphorylated tau (pS199) and of Dyrk1a. The latter is the dual-specificity tyrosine phosphorylation-regulated kinase-1A, a protein kinase that phosphorylates APP and tau and plays an important role in AD neuropathology (Arbones, Thomazeau, Nakano-Kobayashi, Hagiwara, & Delabar, 2019; Branca et al., 2017).

As indicated earlier, APOEε4 is the strongest genetic risk factor for AD (Riedel et al., 2016). Hence, the possibility of a gene-environment interaction has been studied by testing the hypothesis that carriers of one or two of the APOEε4 alleles would be more susceptible to the neurotoxic effects of air pollution (Calderon-Garciduenas et al., 2004). Indeed, APOEε4 carriers exposed to air pollution had greater hyperphosphorylated tau and diffuse Aβ plaques and more pronounced olfactory deficits than APOEε3 carriers (Calderon-Garciduenas et al., 2008; Calderon-Garciduenas et al., 2010; Calderon-Garciduenas et al., 2012). The effects of $PM_{2.5}$, PM_{10}, and NO_x on cognitive functions were more pronounced in female carriers of the APOEε4 allele (Schikowski et al., 2015), and female APOEε4 carriers were also more at risk for air pollution-induced hippocampal metabolic alterations and cognitive deficits (Calderon-Garciduenas, Kulesza, Doty, D'Angiulli, & Torres-Jardon, 2015; Calderon-Garciduenas et al., 2016b). Cacciottolo et al. (2017) also found that the risk of cognitive decline and dementia associated with air pollution was greater in homozygotes for the APOEε4 allele (HR = 3.95), compared to those carrying the APOEε3 allele (HR = 1.65). A recent study of a cohort of older adults in northern Manhattan found that long-term exposure to ambient air pollution was associated with a more rapid cognitive decline and that the association was more pronounced in APOε4 carriers (Kulick et al., 2020). For sake of completeness it should also be mentioned that one study did not find differences between APOE genotypes in susceptibility to air pollution-associated dementia (Wu et al., 2015). The study by Cacciottolo et al. (2017) is the only animal study investigating the role of APOE polymorphism in susceptibility to air pollution-induced AD. They found that a 15-week exposure to nanoparticles increased amyloid plaques significantly more in mice carrying the human APOEε4 gene than in mice carrying the human APOEε3 gene. Given the importance of APOEε4 in AD and the availability of transgenic mouse models, further animal testing under controlled exposure conditions is certainly warranted.

4.4. Parkinson's disease

Air pollution has also been associated with increased risk of PD, though the overall evidence appears to be somewhat less convincing than for AD (Fu, Guo, Cheung, & Yung, 2019;

Kasdagli, Katsouyanni, Dimakopoulou, & Samoli, 2019). PD is a neurodegenerative disorder characterized by a progressive degeneration of dopaminergic neurons in the substantia nigra and of nerve terminals in the striatum. Once loss of dopaminergic neurons has reached about 80%, clinical signs appear, which include resting tremor, rigidity, bradykinesia, and gait disturbances (Cubo & Goetz, 2014). PD is primarily a motor system disorder; however, it also presents olfactory dysfunction, cognitive dysfunction, dementia, and depression. Olfactory dysfunction is an important early effect of PD (Doty, 2012; Mesholam, Moberg, Mahr, & Doty, 1998), and damage to the olfactory bulb seems to precede neuropathology in the motor areas (Braak, Ghebremedhin, Rub, Bratzke, & Del Tredici, 2004). Age is the main risk factor for PD, and prevalence is 1% in people above 60 and 3–5% in those over 85 years (Lema-Tomé et al., 2013); in addition, sex is also a risk factor, as incidence of PD is 90% higher in males than in females (Van Den Eeden et al., 2003). Mutations in several genes (PARK1-PARK13) have been associated with some forms of PD, usually of early onset (before the age of 50) and occurring in family clusters. The great majority of PD cases, however, are sporadic, and may be due to environmental factors or to gene-environment interactions. In addition to the dopamine deficiency resulting from degeneration of dopaminergic neurons in the substantia nigra, protein aggregations in the form of Lewy bodies in surviving neurons of adjacent areas are also a hallmark of PD (Beier & Richardson, 2015). Lewy bodies are a dense core inclusion encircled by a halo of radiating fibrils composed of misfolded α-synuclein. A single point mutation in the α-synuclein gene (PARK1/4) is responsible for the first familial form of autosomal dominant PD (Polymeropoulos et al., 1997; Ulusoy & Di Monte, 2013). Levels of α-synuclein are higher in PD brain than in normal aging (Beier & Richardson, 2015; Ulusoy & Di Monte, 2013).

4.5. Air pollution and Parkinson's disease

A few studies have investigated the possible association between air pollution and PD (see Hu et al., 2019; Kasdagli et al., 2019 for recent reviews and meta-analyses). Kirrane et al. (2015) investigated the incidence of PD among participants in the Agricultural Health Study in two U.S. populations, and found positive associations between PM**2.5** and O_3 and PD in North Carolina, but not in Iowa, possibly because of lower levels of air pollution in the latter state. In another study, Liu, Young, Chen, Kaufman, and Chen (2016) found evidence of an association between PM_{10} and PM**2.5** and PD in female never smokers (smoking has consistently been found to be a protective factor for PD). A case-control study with 1600 PD patients in Denmark suggested that air pollution from traffic sources was associated with a 9% increased risk of PD for each interquartile range increase of NO_2 (2.97 μg/m³), with a higher risk for people living in Copenhagen compared to those living in rural areas (Ritz et al., 2016). In a follow-up study, it was found that in individuals with a functional polymorphism in the gene for the pro-inflammatory cytokine interleukin-1β (IL-1β-rs16944) long-term exposure to NO_x increased PD risk more than in the overall population (Lee et al. 2016a). The rs16944 mutation is in the promoter region of IL-1β and causes enhanced transcription, suggesting that individuals with higher levels of IL-1β may be more susceptible to air pollution neurotoxicity. A study by Lee et al., 2016ain Taiwan also found a positive association between air pollution and PD, particularly for NO_x and CO, but not for PM_{10}. This latter negative finding agrees with the results of a study by Palacios et al. (2014)

in a large (>115,000) cohort of women, part of the Nurses' Health Study, in which no statistically significant associations were found between PM_{10} or **$PM_{2.5}$** and PD. A study examining occupational exposures as risk factor for PD found no association between DE exposure and PD mortality in a large Dutch cohort (Brouwer et al., 2015). Finally, a recent study examined the risk of PD when living near major roads in Ontario, Canada, and found no significant association (Chen et al., 2017), while two other studies found that exposure to $PM_{2.5}$ was associated with a significant increase in hospitalization for PD (Kioumourtzoglou et al., 2016; Zanobetti et al., 2014).

A few studies have examined levels of α-synuclein in post-mortem brains of humans exposed to air pollution (Calderon-Garciduenas et al., 2008; Calderon-Garciduenas et al., 2010; Calderon-Garciduenas et al., 2013). For example, in brains of Mexico City children exposed to high levels of air pollution, particularly in brain regions associated with PD pathology such as olfactory bulb, midbrain, and medulla oblongata, higher levels of α-synuclein were found (Calderon-Garciduenas et al., 2013). These increases in α-synuclein, which were mostly not detected in brains of control children, were paralleled by olfactory dysfunctions in other children living in the same conditions (Calderon-Garciduenas et al., 2010). Olfaction problems have also been reported in individuals exposed to heavy air pollution (Calderon-Garciduenas et al., 2010). Peripheral inflammation (known to be elicited by air pollution) may cause an increase of α-synuclein in the olfactory bulb, and its misfolding and aggregation may spread via the olfactory route, from the olfactory bulb to the midbrain via other olfactory areas and the limbic system (Lema-Tomè et al., 2013). Regarding animal studies, a single controlled study found that exposure of male rats to DE (311 μg/m^3 or higher) for six months increased α-synuclein levels in the midbrain (Levesque et al. 2011b). In another study, an increase in α-synuclein levels was found in the cerebral cortex of C57BL6/J mice (male only) exposed to DE (250 μg/m^3) for three weeks (Coburn et al. unpublished data). In summary, evidence from epidemiological studies suggesting that air pollution may be associated with PD is still limited and further well-planned longitudinal studies are warranted (Fu et al., 2019; Hu et al., 2019; Palacios, 2017).

5. Possible mechanisms underlying air pollution neurotoxicity

Systemic inflammation is a main mechanism by which air pollution causes pulmonary and cardiovascular toxicity (Fiordelisi et al., 2017), and microglia activation, oxidative stress, and neuroinflammation, all induced by air pollution in the CNS, are believed to be causally associated with air pollution-induced neurotoxicity and to be relevant for neurodevelopmental and neurodegenerative diseases (Costa et al., 2014; Costa, Chang, & Cole, 2017b; Costa et al., 2019). Oxidative and inflammatory responses in the CNS following exposure to air pollution have been found in vivo in animals (e.g. MohanKumar et al., 2008; Levesque et al. 2011b; Cole et al., 2016; Bai et al., 2019), in in vitro systems (e.g. Block et al., 2004; Roqué et al., 2016; Milani et al., 2018; Bai et al., 2019), and to a limited extent in humans (Calderon-Garciduenas et al., 2012; Costa, Chang, & Cole, 2017b; Costa et al., 2019). There is substantial evidence demonstrating an important role played by neuroinflammation in neurodevelopmental disorders, particularly ASD (D'Angiulli, 2019; Davis, 2018; Mottahedin et al., 2017). There is also ample evidence that oxidative stress and neuroinflammation occur in several neurodegenerative diseases and contribute to their

etiopathology and progression (Manoharan et al., 2016; Ransohoff, 2016). The following sections will highlight selected aspects that may mechanistically link air pollution with ASD, AD and PD by virtue of oxidative stress and neuroinflammation (for additional discussions please see Costa, 2017; Costa et al., 2019).

5.1. Neurodevelopmental disorders

Microglia play an extremely important role in brain development as these cells contribute to neurogenesis, synaptic pruning, myelination and angiogenesis (Davis, 2018). Yet, excessive microglia activation induced by external factors can cause severe inflammation and be associated with adverse effects in the developing nervous system. For example, microglia-generated pro-inflammatory cytokines have been associated with hypomyelination and ventriculomegaly via toxicity to oligodendrocytes (Allen et al., 2017). As said, inflammation plays an important role in neurodevelopmental disorders, particularly in ASD (Brockmeyer & D'Angiulli, 2016; Prata, Santos, Almeida, Coelho, & Barbosa, 2017; Davis, 2018; D'Angiulli, 2019). Maternal infection (i.e. MIA) causes severe neuroinflammation in the fetus's brain and represents one of the most reliable animal models for ASD (Bilbo, Block, Bolton, Hanamsagar, & Tran, 2018; Patterson, 2011). As discussed below, an increase in pro-inflammatory cytokines may also activate a signaling cascade leading to a decrease in reelin.

5.1.1. Disruption of reelin homeostasis—Secreted in the marginal zone of the developing cerebral cortex, reelin is a signaling glycoprotein known to play an important role in neuronal migration and establishment of neuronal polarity (Folsom & Fatemi, 2013; Förster, 2014; Jossin, 2004; Sekine, Kubo, & Nakajima, 2014). The canonical reelin signaling pathway is activated upon binding of reelin to the VLDL (very low-density lipoprotein) receptor and APOE receptor 2, which triggers tyrosine phosphorylation of the intracellular adaptor protein disabled-1 (Dab1). Phosphorylated Dab1 then activates a kinase cascade involving PI-3 kinase, LIM kinase-1, and several others (Förster, 2014). Such complex networks of signaling pathways mediate the ultimate effects of reelin on neuronal migration and polarity in the developing brain. Several lines of evidence suggest an involvement of reelin in ASD. Reelin expression is significantly decreased in brain from individuals with ASD (Fatemi et al., 2005; Folsom & Fatemi, 2013), and the reelin gene (*RELN*) is affected in several autistic pedigrees (Lammert & Howell, 2016; Persico et al., 2001; Serajee, Zhong, & Huq, 2006; Wang et al., 2014), as is the methylation pattern at the reelin gene promoter (Lintas, Sacco, & Persico, 2016). Mice lacking the C-terminal region of reelin exhibit behavioral abnormalities related to ASD (Sakai, Shoji, Kohno, Miyakawa, & Hattori, 2016), as does the reeler ($rl^{-/-}$) mouse (Katsuyama & Terashima, 2009; Reiner, Karzburn, Kshirsagar, & Kaibuchi, 2016). In addition, cortical disorganization has been reported in reelin-deficient mice and in ASD patients, and dysregulation of reelin-driven cortical neuron migration is present in ASD, as evidenced by cortical disorganization (Stoner et al., 2014; Boyle et al., 2011; Reiner et al., 2016). Furthermore, a decrease of reelin protein and mRNA levels are found in the MIA model of ASD (Ghiani et al., 2011; Meyer et al., 2006), and *N*-acetylcysteine completely prevents lipopolysaccharide (LPS)-induced decreases of reelin (Novais et al., 2013). Chang et al. (2019) found that developmental DE exposure of mice (250–300 μg/m^3 from GD0 to PND21), which induces ASD-like

behavioral alterations (Chang et al., 2018), causes neuroinflammation (increased IL-6), increases in pSTAT3 and DNA methyltranferase-1 (DNMT1), and a decrease in reelin expression. Structural abnormalities in cerebral cortical layering as observed in ASD (Stoner et al., 2014) were also found (Chang et al., 2019; Cole et al. submitted). Fig. 1 shows a possible mechanism for cortical disruption induced by developmental exposure to DE in mice.

5.1.2.   Excitatory/inhibitory imbalance—An imbalance of excitatory/inhibitory neurotransmission is believed to be relevant in ASD (Uzunova, Pallanti, & Hollander, 2016). The hypothesis of an increased excitation/inhibition ratio was first formulated by Rubenstein and Merzenich (2003) and has influenced research in this area since then. More recently, however, such imbalance, which is found in all animal models of ASD, has been suggested as a compensatory mechanism rather than a causative one in ASD (Antoine, Langberg, Schnepel, & Feldman, 2019). Such imbalance may be due to a reduced GABAergic action or to an increased glutamatergic one, though in individuals with ASD the deficit appears to consist in a reduced GABAergic action (Robertson, Ratai, & Kanwisher, 2016). By inducing neuroinflammation, and specifically by increasing levels of IL-6, air pollution would also increase expression of DNMT1 (Chang et al., 2019). DNMT1 decreases the expression of GAD 67 (glutamic acid decarboxylase 67), and hence inhibitory GABAergic neurotransmission, thereby disrupting the balance of excitation/inhibition, as also found in ASD and in mouse models of ASD (Han et al., 2012). Of interest is that MIA also causes a decrease of GAD67 (Nouel, Burt, Zhang, Harvey, & Boksa, 2012).

5.1.3.   Changes in the microbiota—The existence of a vast number of microbes in the body has been known for centuries, but only recently has the microbiota been recognized to play important roles in various diseases including diseases of the CNS (Bell et al., 2019; Dinan & Cryan, 2017; Kim, Jeon, & Chun, 2013; Tillisch, 2014). While microbiota in the nasal cavity, the oral cavity and the lungs exist, the gut microbiota are the most studied in relation to possible dysbiosis and disease (Bell et al., 2019). Earlier indications suggested that in humans, gut microbes outnumbered cells by 10:1; however, more recent studies have questioned this ratio and indicate one much lower (Sender, Fuchs, & Milo, 2016). The microbiota is composed of over 1000 species of bacteria (mostly anaerobic) with over 7000 strains; the most common microorganisms are Bacteroidetes and Firmicutes (Bell et al., 2019). Colonization of the gut begins at birth, and the microbiota change with aging. Gut microbes are essential to digestion and absorption of nutrients and play important role in normal physiology. Dysbiosis of the gastrointestinal tract has been implicated in the development of various disorders, such as GI tract inflammation, but also obesity, type 2 diabetes mellitus, as well as neurodevelopmental and neurodegenerative disorders. Some information on the role of the gut microbiota in CNS disorders has been obtained using germ-free mice or the administration of antibiotics. A gut-brain axis clearly exists by which gut microbiota influence the brain (Bell et al., 2019; Warner, 2019). Such communication can be mediated by multiple pathways such as vagal afferent nerves, immune and HPA axis modulation, and production of active metabolites (Tillisch, 2014). There is evidence that diet, drugs and environmental agents can cause dysbiosis, i.e. change the composition of gut microbiota (Rosenfeld, 2017). Several studies in humans and animals have shown that air

pollution can affect the gut microbiota by changing its composition (Alderete et al., 2018; Mutlu et al., 2018; Salim, Kaplan, & Madsen, 2014; Valles & Francino, 2018). Parallel evidence also indicates that dysbiosis of the gut microbiota plays an important role in ASD(Ding, Taur,&Walkup, 2017; Hughes, Rose, & Ashwood, 2018). In genetic and environmental models of ASD (e.g. the BTBR mouse, the valproic acid model, or the MIA model) changes in gut microbiota have been found to parallel the behavioral dysfunctions, and administration of selected deficient bacteria can reverse such impairments (Hsiao et al., 2013; Sgritta et al., 2018).

5.2. Neurodegenerative diseases

There is ample evidence that oxidative and neuroinflammatory processes occur in various neurodegenerative diseases and contribute to their etiopathology (Butterfield & Halliwell, 2019; Heneka, McManus, & Latz, 2019; Manoharan et al., 2016; Ransohoff, 2016). Oxidative stress and neuroinflammation play a cardinal role in AD (Heneka et al., 2015; Huang, Zhang, & Chen, 2016; Moulton & Yang, 2012; Rubio-Perez & Morillas-Ruiz, 2012). Neuro-inflammation can contribute to amyloid toxicity (Minter, Taylor, & Crack, 2016), and ApoEε4 (a strong genetic risk factor for AD) is less protective against neuro-inflammation (Tai et al., 2015). Activation of microglia causes both an increase in oxidative stress and in pro-inflammatory cytokines. Oxidative stress is believed to play a role in PD pathogenesis and has been shown to cause α-synuclein aggregation (Takahashi et al., 2007), and microglia activation and neuroinflammation plays a central role in the pathogenesis of PD (Anderson, Coffey, Berwin, & Havdra, 2018; Hirsch, Vyas, & Hunot, 2012; Lull & Block, 2010; Qian, Flood, & Hong, 2010). An additional aspect that needs to be considered is the contribution of peripheral inflammation to neuroinflammation. Though different from central inflammatory processes (Filiou, Arefin, Moscato, & Graeber, 2014), systemic inflammation affects inflammatory processes in the CNS (Hopkins, 2007; Lema-Tomè et al., 2013; Mumawet al., 2006). As indicated earlier, peripheral inflammation is a cardinal effect of exposure to air pollution (Anderson et al., 2012). Thus, the contribution of peripheral inflammatory processes to adverse CNS effects needs to be further investigated.

More specific hypotheses which may mechanistically link air pollution and neurodegeneration, particularly AD, are also being investigated; these include, for example, changes in miRNAs or in telomere length (Jardim, 2011; Miri et al., 2019). Most have been discussed in detail recently (Costa, 2017), while some of the compelling ones are briefly discussed below. Another very interesting potential mechanism has been recently proposed by Cacciottolo et al. (2020). Exposure of mice to TRAP-PM$_{0.2}$ (300 μg/m^3) or of neuronal cells to the same nanoparticles (1–10 μg/ml) caused an increase in oxidative stress in lipid rafts associated with an increase in Aβ; the latter was inhibited by the antioxidant *N*-acetyl cysteine, suggesting that oxidative damage may represent an important event in the pro-amyloidogenic effects of air pollution.

5.2.1. Disruption of adult neurogenesis—Findings from post-mortem human brains and from animal studies have shown that adult neurogenesis is impaired in neurodegenerative diseases (Horgusluoglu, Nudelman, Nho, & Saykin, 2017), including AD (Fuster-Matanzo, Llorens-Martin, Hernandez, & Avila, 2013) and PD (Marxreiter,

Regensburger, & Winkler, 2013). Alterations in adult neurogenesis differ among different neurodegenerative diseases but are believed to be relevant to their progression. Thus, for example, impairment of adult neurogenesis in the hippocampal region may be associated with decreased cognitive function in AD (Fuster-Matanzo et al., 2013; Horgusluoglu et al., 2017). It has been reported that brain inflammation inhibits basal neurogenesis in the hippocampal subgranular zone, an effect that is prevented by minocycline, an inhibitor of microglia activation (Carpentier & Palmer, 2009; Ekdahl, Claasen, Bonde, Kokaia, & Lindvall, 2003). Evidence of decreased adult neurogenesis following early postnatal inflammation in rodents has also been reported (Dinel et al., 2014; Lajud & Torner, 2015). Given that a main effect of air pollution in the brain is neuro-inflammation, it is conceivable that exposure may result in an impairment of adult neurogenesis. In agreement with this hypothesis, it has been reported that exposure of adult mice to DE (250–300 $\mu g/m^3$ for 6 h) caused oxidative stress and neuro-inflammation, and decreased adult neurogenesis in mice, particularly in males (Coburn et al., 2018). These findings suggest that air pollution, by virtue of its ability to cause neuro-inflammation, can disrupts the process of adult neurogenesis and may thus contribute to the etiopathology of neurodegenerative diseases.

5.2.2. Alterations of reelin—As for ASD, there is also evidence of an involvement of reelin in AD, and air pollution-induced alterations in reelin expression and/or signaling may indeed play a relevant role in the observed association between exposure and AD. In the adult CNS, reelin is expressed in GABAergic interneurons in the cortex and hippocampus, where it modulates learning and memory processes. Reelin provides functions via proteolytic activity as a serine protease, and via activation of specific receptors which elicit signaling cascades (Bock & May, 2016; Förster, 2014). Brain reelin levels are decreased in natural aging (Stranahan, Haberman, & Gallagher, 2011), in transgenic animal models of AD (Chin et al., 2007; Kocherhans et al., 2010; Mota, Ferreira, & Rego, 2014b; Yu, Tan, Yu, Xie, & Tan, 2016), and in brains of AD patients, particularly in the early stages (Chin et al., 2007; Herring et al., 2012). Reelin mRNA is instead up-regulated in later stages of AD (Botella-Lopez et al., 2010), which may reflect a potential compensatory mechanism or an effect of advanced disease processes (Yu et al., 2016). However, though increased, in these later stages reelin is less effective, as β-amyloid compromises reelin signaling in late AD (Cuchillo-Ibanez et al., 2016). Reelin can indeed inhibit Aβ generation and promote Aβ clearance (Kocherhans et al., 2010; Pujadas et al., 2014), and low levels of reelin are associated with higher tau phosphorylation (Yu et al., 2016). In addition, decreased reelin levels may contribute to the initiation and progression of AD by impairing synaptic functions, cytoskeleton stability, and proper axonal transport (Yu et al., 2016). Reelin is known to play an important role in synaptic plasticity, by stimulating long term potentiation through modulation of NMDA receptors (Weeber et al., 2002), and decreased reelin levels would cause synaptic dysfunction in the hippocampus, leading to memory and cognitive deficits which may precede neuronal loss, as found in AD (Ma & Klann, 2012; Yu et al., 2016). A transcriptomics analysis of the AD brain found that synapse-associated pathways were the most affected, and among these, reelin signaling was one of the few that was significantly altered (Karim et al., 2014). A genome-wide study in elderly, non-demented individuals identified three single nucleotide polymorphisms in the reelin gene (*RELN*) that significantly correlated with increased tau phosphorylation and concomitant appearance of

neurofibrillary tangles (Kramer et al., 2010). In addition, a more recent study found that, among men, genetic polymorphisms of *RELN* were associated with AD (Feher, Juhasz, Pakaski, Kalman, & Janka, 2015). Overall, decreased reelin levels and signaling appear to be key early events in AD. Hence, experiments aimed at increasing reelin signaling in the CNS to counteract the development of AD have already been underway. For example, in one study, purified recombinant reelin injected into the ventricles increases synaptic function and cognitive abilities of wild-type mice (Rogers et al., 2011). Similarly, exogenous reelin prevented cognitive deficits induced by phencyclidine in mice (Ishii et al., 2015). For interference with reelin homeostasis to represent a mechanism for air pollution in AD, exposure should lead to a decreased expression/signaling of reelin. Neuroinflammation (and specifically an increase in 1L-6) which follows microglia activation, is increased by air pollution (Block & Calderon-Garciduenas, 2009; Cole et al., 2016). As indicated earlier, 1L-6 stimulates theJAK/STAT3 pathway which increases DNMT1 (Garbers, Aparicio-Siegmund, & Rose-John, 2015; Shaun & Thomas, 2012), causing increased methylation of the reelin promoter and a decrease in reelin expression (Noh et al., 2005; Palacios-Garcia et al., 2015). As described in an earlier section, this pathway was activated upon developmental exposure to DE (Chang et al., 2019) (Fig. 4). Another study reported that exposure to the anesthetic sevoflurane increased DNMT1, caused hyper-methylation of *RELN*, a decrease of reelin mRNA and protein, and associated cognitive impairment (Ju et al., 2016). Interestingly, MIA (elicited by infection during pregnancy), which leads to offspring that display neuroinflammation, has been shown not only to decrease levels of reelin protein and mRNA in brain of offspring (Ghiani et al., 2011; Novais et al., 2013), but also to drive AD-like neuropathology as the animal ages (Krstic et al., 2012). The notion that neuroinflammation (and oxidative stress) may play an important role in modulating reelin expression is also supported by studies showing that *N*-acetylcysteine completely prevents lipopolysaccharide (LPS)-induced decreases of reelin (Novais et al., 2013). Since impairment of reelin expression and signaling are known to occur in autism and have been found in mice upon developmental exposure to DE (Costa, Cole, et al., 2017a; Chang et al., 2019), the suggestion that ASD and AD may share some genetic and/or etiopathological aspects may be of relevance (Khan et al., 2016), and warrants further investigations.

5.2.3. Alterations in glutamate homeostasis—The correct functioning of glutamatergic synapses is essential for learning and memory, and disruptions of glutamate homeostasis may play a relevant role in neurological/neurodegenerative disorders (Zhang, Li, Feng, & Wu, 2016). Alterations in glutamate receptors, particularly the ionotropic NMDA (*N*-methyl-ᴅ-aspartate) receptors, but also metabotropic receptors, occur in AD, leading to over-activation of the glutamatergic system (Mota, Ferreira, & Rego, 2014b; Lewerenz & Maher, 2015; Rudy, Hunsberger, Weitzner, & Reed, 2015; Ribeiro, Vieira, Pires, Olmo, & Ferguson, 2017). In addition, glutamate transporters, particularly in astrocytes, are altered in AD, leading to dysregulation of the tightly controlled glutamate levels in the extracellular milieu, and contributing to an overstimulation of the glutamatergic system (Murphy-Royal, Dupuis, Groc, & Oliet, 2017; Rudy et al., 2015). Limited evidence from animal and in vitro studies suggests that air pollution may interact with the glutamatergic system. A study by Win-Shwe et al. (2009) reported that exposure of mice to nanoparticle-enriched DE for four weeks caused an increase of the NR1 (now GluN1)

subunit of the NMDA receptor in the olfactory bulb. Two other studies reported that exposure of mice to nanoparticles induced a decrease of GluN1 in the hippocampus (Cacciottolo et al., 2017; Morgan et al., 2011). All three studies found that other NMDA receptor subunits were unchanged. The significance of these findings in relationship to air pollution/AD is still unclear. Win-Shwe et al. (2009) also found that DE exposure increased the levels of free glutamate in the olfactory bulb, in agreement with results obtained by various investigators in vitro. Liu et al. (2015) found that $PM_{2.5}$ caused the release of glutamate from microglia; excess glutamate would then over-activate NMDA receptors on neurons leading to neuronal death. The increase in glutamate appeared to be due to an increase in the activity and release from microglia of glutaminase (which converts glutamine to glutamate) (Liu et al., 2015). In an earlier study, Ye et al. (2013) reported that pro-inflammatory cytokines could increase glutaminase activity and glutamate levels in neurons. Furthermore, Barger, Goodwin, Porter, and Beggs (2007) found that microglia activation (by lipopolysaccharide) caused an increased release of glutamate. They suggested that the initial oxidative stress, particularly lipid peroxidation, would cause glutathione (GSH) depletion, which would be compensated for with an increased activity of the cysteine-glutamate exchanger, leading to increased extracellular glutamate. These findings indicate that neurodegenerative consequences of neuroinflammation may result from the conversion of oxidative stress to excitotoxic stress (Barger et al., 2007). Whatever the exact mechanism (s), it would appear that air pollution may increase extracellular levels of glutamate, and this may indeed contribute to neurotoxicity observed in AD and possible other neurodegenerative diseases.

5.2.4.   Changes in the microbiota—In addition to its potential role in neurodevelopmental disorders such as ASD, gut dysbiosis appears also to be involved in neurodegenerative diseases such as AD and PD (Bell et al., 2019; Dinan & Cryan, 2017; Warner, 2019). Changes in the gut microbiome have been found in AD and in experimental models of AD (Jiang, Li, Huang, Liu, & Zhao, 2017; Xu & Wang, 2016). For example, mice overexpressing APP have attenuated microglia activation and decreased Aβ deposition if raised in germ-free-conditions (Harach et al., 2017). Metabolites of gut microbes, such as short chain fatty acids (SCFA, such as acetate, propionate, butyrate), have also been shown to activate microglia and increase neuroinflammation (Warner, 2019). Similar findings have been reported in α-synuclein-overexpressing mice, in which germ-free conditions attenuate motor deficits and brain pathology, suggesting a role played by gut microbiota in PD (Sampson et al., 2016).

6.   Conclusions

While, for years, studies on adverse effects of air pollution have been focused first on the respiratory system, then on the cardiovascular system, the past decade has seen a substantial interest in the potential effects of air pollution on the CNS. CNS disorders in the general population are of great concern and appear to be increasing, because of better diagnoses and/or the aging of the population, but also because many may involve environmental factors in their etiopathogenesis. Most studies focusing on air pollution have examined the effects of exposure during development (both pre- and early postnatally) and in the elderly, as these

two populations appear to be the most sensitive to air pollution-induced neurotoxicity. Alterations in several neurobehavioral functions have been found in children exposed to high levels of air pollution, and evidence of increased depression and cognitive impairment have been found in adults and in the elderly. Specific CNS disorders have also been shown to be associated with exposure to air pollution, namely ASD as a neurodevelopmental disorder, and AD (in particular) and PD among the neurodegenerative diseases. The great majority of epidemiological studies have revealed positive associations, and the null or negative studies are only a handful. Nevertheless, several limitations remain regarding the human studies. Possibly the most important one relates to the characterization and quantification of the exposure, as often it is based on models considering location of housing, which may provide inaccurate exposure estimations. Indeed, the issue of exposure, in both qualitative and quantitative terms, remains a key element that should guide the design of future epidemiological studies. A better knowledge of exposure would allow for example, an understanding of whether different outcomes in different populations may be related to subtle differences in exposure parameters. In general, $PM_{2.5}$ appears to be the most significant component of air pollution associated with adverse CNS outcomes, while NO_x or O_3 have provided more contrasting results. However, as discussed earlier, UFPM (which are comprised in the mass of $PM_{2.5}$) are believed to be most important PM for neurotoxicity, because of their biological characteristics and their ability to gain access to the CNS. Yet, the number of UFPM is rarely quantified in most studies. Furthermore, elemental contaminants such as iron or sulfur, associated with UFPM, may play important, and not yet recognized roles in determining adverse effects on the CNS (Cory-Slechta et al., 2019). it is not clear whether there are additive and/or synergistic effects among air pollution components.

Confounding factors, from socioeconomic status to smoking or other health conditions, are always important aspects to consider. When studying effects of air pollution in adults and in aging individuals, the relevant time of exposure (i.e. early in life, during adulthood, etc.) also represents a dilemma. For example, when considering the contribution of air pollution to neurodegenerative diseases such as AD, what are the significant "windows of susceptibility" for air pollution exposure? Is it the developmental period (pre- and post-natal), in tune with the Barker hypothesis of early origin of late-life diseases? Similar biochemical/molecular alterations observed in ASD and AD suggest that this area of mechanistic research may provide important new information in this regard, and controlled experimental studies are underway to specifically investigate whether developmental exposures may facilitate late behavioral, biochemical and morphological signs of AD (Cole et al. in progress). Is a prolonged, multidecade exposure necessary or sufficient (even at low levels), as also suggested by some studies (e.g. Kulick et al., 2020) ? Or is a late-life exposure enough to precipitate CNS disease (e.g. Younan et al., 2020)? While difficult to assess in epidemiological studies, these variables could be studied in animals under controlled exposure conditions. Indeed, having established that air pollution is associated with poor brain health, what are needed now are high quality longitudinal cohort studies with large sample size and detailed knowledge of residential history, employment, and mobility (Russ et al., 2019).

One important aspect of the research portfolio on air pollution and brain health is that there is a rather strong convergence of findings in human epidemiological and in experimental

animal studies (Costa et al., 2014). This is extremely encouraging, as controlled animal exposure would allow an understanding of the mechanism(s) that may underlie observed behavioral effects. Animal studies would further the understanding of the most significant component of air pollution associated with adverse CNS effects, and this in turn may allow very specific and targeted interventions aimed at prevention. Mechanistic studies are certainly warranted, as they may increase our understanding of CNS effects associated with air pollution and may also lead to potential therapeutic interventions. The recent experimental study by Cacciottolo et al. (2020) is very promising in this regard. Limited in vitro experiments also point to the effects of air pollutants on microglia activation, oxidative stress and neuroinflammation, which appear to be the key responses to air pollution in the CNS. Thus, in vitro approaches may also contribute to our overall understating of air pollution neurotoxicity.

Needless to say, such research efforts must go hand in hand with measures to reduce man-made air pollution. As discussed earlier, TRAP is a major contributor to air pollution, and measures to reduce DE exposures and converting to less-polluting means of transportation are important ways to address this problem. Pollution caused by the processes of rapid industrialization and urbanization is considered highly relevant for air pollution in countries like China, where it has led to some of the worst AQI in the world. Measures to curb pollution have been already implemented in this country, but several challenges remain for the future (Zeng, Cao, Qiao, Seyler, & Tang, 2019). Acknowledgment that there is an urgent need to reduce urban pollution is also recognized in India, where some megacities see levels of $PM_{2.5}$ several fold higher than the WHO recommended limits for extended periods of time (Patel, 2019).

Acknowledgments

Abbreviations:

Aβ	Amyloid beta
AD	Alzheimer's disease
ADHD	Attention Deficit Hyperactivity Disorder
APP	Amyloid Precursor Protein
AQI	Air Quality Index
ASD	Autism Spectrum Disorder
BACE	Beta-site APP-Cleaving Enzyme
CNS	Central Nervous System
CO	Carbon Monoxide

COX	Cyclooxygenase
CSF	Cerebrospinal Fluid
DE	Diesel Exhaust
DNMT	DNA Methyltransferase
EPA	Environmental Protection Agency
EU	European Union
FA	Filtered Air
GD	Gestational Day
GFAP	Glial Fibrillary Acidic Protein
HR	Hazard Ratio
IL	Interleukin
MCI	Mild Cognitive Impairment
MIA	Maternal Immune Activation
NOx	Nitric Oxides
NO$_2$	Nitrogen Dioxide
O$_3$	Ozone
OR	Odds Ratio
PD	Parkinson's Disease
PM	Particulate Matter
PND	Postnatal Day
PPB	Parts per Billion
PSEN	Presenilin
RELN	Reelin
SO$_2$	Sulfur Dioxide
TRAP	Traffic Related Air Pollution
VLDL	Very Low-Density Lipoprotein

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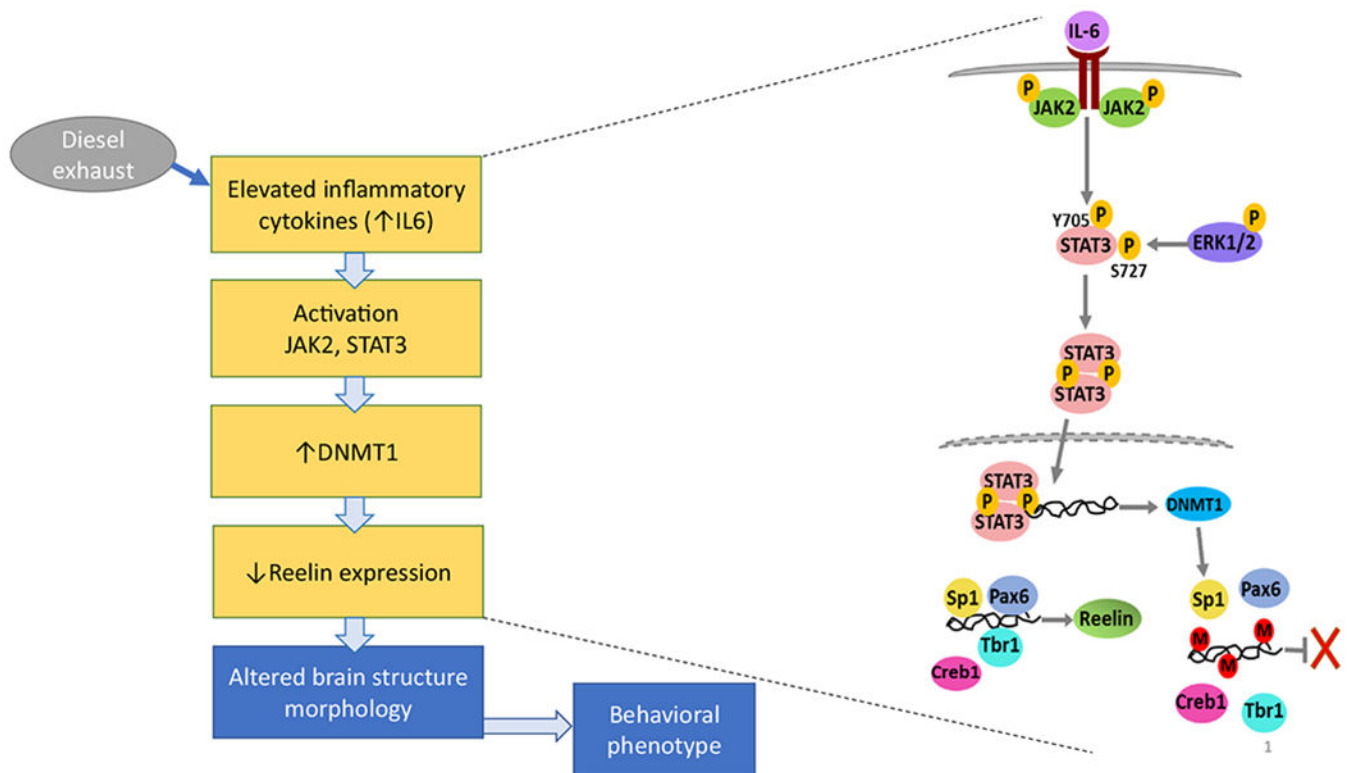**Fig. 1.**
Possible mechanism for developmental DE exposure-induced cortical disruption.
Developmental exposure of mice to DE (250 μg/m^3, from GD 1 to PND 21) causes
neuroinflammation, as evidenced by elevated levels of IL-6. This in turn activates STAT3
which acts as a transcription factor and up-regulates DNMT1 expression, leading to
decreased reelin levels. Known for its critical role in guiding the process of neuronal
migration during development, decreased expression of reelin during critical expression
periods leads to altered cortical structures (Chang et al., 2019), as observed in ASD (Stoner
et al., 2014). The same developmental DE exposure causes significant alterations in all three
behavioral domains of ASD (communication, repetitive behavior, social interactions) (Chang
et al., 2018). Figure reproduced from Chang et al. (2019) with permission.

Table 1

Air quality standards in the U.S. and in the E.U.

Pollutant	Averaging period	U.S.	E.U.
Sulfur dioxide	1 h	75 ppb	350 μg/m^3
Carbon monoxide	8 h	10 mg/m^3	10 mg/m^3
Ozone	8 h	0.07 ppm	120 μg/m^3
Nitrogen dioxide	1 h	100 ppb	200 μg/m^3
PM$_{2.5}$	1 year	15 μg/m^3	25 μg/m^3
PM$_{10}$	1 day	150 μg/m^3	50 μg/m^3
Lead	1 year	0.15 μg/m^3	0.5 μg/m^3

Table 2

Air Quality Index (AQI) in the U.S.A.

AQI values	Levels of health concerns	Color
0–50	Good	Green
51–100	Moderate	Yellow
101–150	Unhealthy for sensitive groups	Orange
151–200	Unhealthy	Red
201–300	Very Unhealthy	Purple
301–500	Hazardous	Maroon