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Developmental impact of air pollution on brain function

Lucio G. Costa[a,b,*], Toby B. Cole[a,c], Khoi Dao[a], Yu-Chi Chang[a,1], Jacqueline M. Garrick[a]

[a] Dept. of Environmental and Occupational Health Sciences, University of Washington, Seattle, WA, USA
[b] Dept. of Medicine & Surgery, University of Parma, Italy
[c] Center on Human Development and Disability, University of Washington, Seattle, WA, USA

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ABSTRACT

Air pollution is an important contributor to the global burden of disease, particularly to respiratory and cardiovascular diseases. In recent years, evidence is accumulating that air pollution may adversely affect the nervous system as shown by human epidemiological studies and by animal models. Age appears to play a relevant role in air pollution-induced neurotoxicity, with growing evidence suggesting that air pollution may contribute to neurodevelopmental and neurodegenerative diseases. Traffic-related air pollution (e.g. diesel exhaust) is an important contributor to urban air pollution, and fine and ultrafine particulate matter (PM) may possibly be its more relevant component. Air pollution is associated with increased oxidative stress and inflammation both in the periphery and in the nervous system, and fine and ultrafine PM can directly access the central nervous system. This short review focuses on the adverse effects of air pollution on the developing brain; it discusses some characteristics that make the developing brain more susceptible to toxic effects, and summarizes the animal and human evidence suggesting that exposure to elevated air pollution is associated with a number of behavioral and biochemical adverse effects. It also discusses more in detail the emerging evidence of an association between perinatal exposure to air pollution and increased risk of autism spectrum disorder. Some of the common mechanisms that may underlie the neurotoxicity and developmental neurotoxicity of air pollution are also discussed. Considering the evidence presented in this review, any policy and legislative effort aimed at reducing air pollution would be protective of children's well-being.

1. Air pollution

In December 1952, a dense smog containing sulfur dioxide and smoke particulate (from coals burning and industrial activities) descended upon London, resulting in a very high morbidity and mortality (Bell and Davis, 2001; Anderson et al., 2012). This episode, and various others, prompted awareness that quality of air is an important determinant of human health. In 1970 regulation was enacted in the U.S. (the Clean Air Act), and limits were set for six primary air pollutants, carbon monoxide, lead, nitrogen dioxide, ozone, sulfur dioxide, and particulate matter (PM). Sources of these compounds are motor vehicles, construction equipment, electric utilities, and industrial facilities. Ozone is formed when nitrogen oxides react with volatile organic carbons and oxygen in the presence of heat and light, while sulfur dioxide is formed when sulfur-containing fuel is burned. 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 (e.g. volcanoes, fires) or of man-made sources (e.g. tobacco smoke, 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 $< 10\,\mu m$ in diameter, while $PM_{2.5}$ represents particles $< 2.5\,\mu m$ in diameter (fine PM). Also, of relevance (particularly regarding neurotoxicity) is ultrafine PM (UFPM or $PM_{0.1}$, with diameter $< 100\,nm$).

Ambient air pollution is continuously monitored by regulatory agencies in various countries, and most particulate information is available for $PM_{2.5}$. The Air Quality Index provides information on levels of air pollutants, and in some cases on their potential adverse effects. Its specific definition varies among countries but in general it varies between 0 and 500, with values below 50 considered acceptable and values over 150–200 considered to be unhealthy. In some urban areas (e.g. large cities in India, China or Mexico) the Air Quality Index may remain above 200 for several days and even exceed it. Traffic-related air pollution (TRAP) is a major contributor to global air

* Corresponding author. Department of Environmental and Occupational Health Sciences, 4225 Roosevelt Way NE, Suite 100, University of Washington, Seattle, WA, 98105, USA.
E-mail address: lgcosta@uw.edu (L.G. Costa).
[1] Present address: Gradient Corporation, Seattle, WA.

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pollution, of which diesel exhaust (DE) is an important component (Ghio et al., 2012). In New Delhi, it is estimated that traffic may contribute to up to 72% of air pollution (Goyal et al., 2006). 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 traffic-related air pollution. In addition to PM, DE contains more than forty toxic air pollutants, including nitrogen and sulfur oxides, carbon monoxide, hydrocarbons, volatile organic compounds, metals, organic and elemental carbon, and its makeup varies by engine load conditions and fuel composition (Cooney and Hickey, 2008; Lim et al., 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 PM, nitrogen oxides, volatile organic compounds, sulfur oxide and carbon monoxide (Su et al., 2008).

Inhalation is the main exposure route for air pollutants. While PM_{10} is filtered out by the nose and upper airways, $PM_{2.5}$ is deposited in the lungs or ingested (Forman and Finch, 2018). $PM_{2.5}$ can enter the olfactory epithelium and be transported in the olfactory bulb, and then further to the olfactory cortex and other brain regions (Ajmani et al., 2016). Oberdoerster and his colleagues (Oberdoerster and Utell, 2002; Oberdoerster et al., 2004) have shown that UFPM 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 and from there to the brain (Forman and Finch, 2018). The first and most studied target for air pollution toxicity are the airways; nose and throat irritation, bronchoconstriction and dyspnea are observed, particularly in individuals with pre-existing respiratory conditions (Kampa and Castanas, 2008). PM that penetrates the alveolar epithelium and ozone are responsible for lung inflammation and, together with metals, may also induce emphysema and lung cancer (Pope and Dockery, 2006). The cardiovascular system has also emerged in the past two decades as an important target for air pollution toxicity (Brook and Rajagopalan, 2007; Brook et al., 2010), as systemic inflammatory changes caused by air pollution affect blood coagulation, atherosclerosis progression, and are associated with consistent increased risk for cardiovascular events (Pope and Dockery, 2006; Brook and Rajagopalan, 2007; Brook et al., 2010).

2. Neurotoxicity of air pollution

In recent years mounting evidence indicates the central nervous system (CNS) as a primary important target of air pollution. As indicated before, inhaled UFPM may enter the CNS either by way of the olfactory nerve, or through the endothelial junctions that comprise the vascular interface of the blood-brain barrier, rendered more permeable by higher levels of peripheral oxidative stress and inflammation (Lochhead et al., 2010). As discussed in several reviews, human epidemiological and animal studies suggest that air pollution may negatively affect the CNS and contribute to CNS diseases (Calderon-Garciduenas et al., 2002; Block and Calderon-Garciduenas, 2009; Genc et al., 2012; Block et al., 2012; Costa et al., 2014, 2017a; Sram et al., 2017; Russ et al., 2019). Decreases in cognitive and olfactory functions, auditory deficits, depressive symptoms and other adverse neuropsychological effects have been reported in children, adults and the elderly (Ranft et al., 2009; Freire et al., 2010; Calderon-Garciduenas et al., 2010, 2011; Fonken et al., 2011; Guxens and Sunyer, 2012; Lee et al., 2019), where increased markers of oxidative stress and neuroinflammation have been found in postmortem investigations (Calderon-Garciduenas et al., 2008, 2011; 2012; Levesque et al., 2011a). Animal studies are supportive of the human observations (Costa et al., 2014). For example, dogs exposed to heavy air pollution had signs of neuroinflammation 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). Controlled exposure to DE has been reported to alter motor activity, spatial learning and memory, novel object recognition ability, and emotional behavior, and to cause microglia activation, oxidative stress and neuro-inflammation in the CNS (MohanKumar et al., 2008; Gerlofs-Nijland et al., 2010; Win-Shwe and Fujimaki, 2011; Levesque et al., 2011b; Ehsanifar et al., 2019; Cole et al., 2016). Evidence accumulated so far strongly indicates that air pollution negatively affects the CNS, and of much interest is whether it may be causally associated with neurological or neuropsychiatric disorders, particularly neurodevelopmental and neurodegenerative diseases. Several epidemiological studies identifying adverse effects of air pollution on behavior, particularly cognitive behavior, have identified significant effects in the elderly (Ranft et al., 2009; Power et al., 2011; Weuve et al., 2012; Chen et al., 2015). Aging is often associated with a wide variety of clinical and pathological conditions which can be generally classified as neurodegenerative diseases (e.g. Alzheimer's disease (AD), or Parkinson's disease (PD)). There is only limited evidence from epidemiological studies suggesting that air pollution may be associated with PD, though observations in humans and in controlled animal studies suggest that air pollution may increase the expression of the PD marker α-synuclein (Costa, 2017). In contrast, evidence is stronger for an association between elevated air pollution and AD, as indicated by epidemiological and experimental studies (Power et al., 2016; Costa, 2017). As age appears to represent a significant determinant of air pollution neurotoxicity, several investigators have focused on effects of perinatal (pre- and post-natal) air pollution exposure on brain development and on possible associations with neurodevelopmental disorders. The following sections will discuss the general characteristics that render the developing brain extremely sensitive to external insult, and the current knowledge on the effect of air pollution on brain development, with a focus on a major neurodevelopmental disorder, autism spectrum disorder (ASD). This is not a systematic review and does not include evaluation of the risk of bias or quantitative evaluation of the evidence.

3. The sensitivity of the developing central nervous system to environmental insult

Several lines of evidence suggest that the developing nervous system may be more susceptible, and/or differentially susceptible, to toxic insult than the adult nervous system. Different parts of the CNS develop at different stages; cell proliferation, migration and differentiation contribute to the formation of definite brain structures, in which the correct number of cells in the proper location is necessary for proper function (Bayer et al., 1993; Rodier, 1994). Even within a single brain region, subpopulations of neurons may have different rates of development; for example, in the cerebellum, Purkinje cells develop early (embryonic days 13–15 in the rat, corresponding to gestational weeks 5–7 in humans), while granule cells are generated much later (postnatal days 4–19 in the rat, corresponding to gestational weeks 24–36) (Bayer et al., 1993). Failure in cell proliferation or cell migration because of exposure to toxic insults has profound deleterious effects on the developing brain (Costa et al., 2004). Though neurons maintain the ability to make new synapses throughout life, the period of brain development when synaptogenesis occurs is critical for the formation of the basic circuitry of the nervous system (Rodier, 1995). Furthermore, in the developing nervous system, neurotransmitters may have functions other than neurotransmission, such as modulation of cell proliferation, survival, and differentiation (Nguyen et al., 2001), and toxicants that interfere with neurotransmission during development may cause permanent defects in the CNS. Developmental neurogenesis produces more neurons than those found in the mature nervous system, and excess neurons are pruned by finely regulated apoptotic processes at different developmental times (Johnson and Deckwerth, 1993). Any chemical interfering with apoptotic processes may trigger degeneration of neurons that would not otherwise have been deleted or may promote survival of unnecessary cells (Ikonomidou et al., 2001). In addition, pruning, defined as loss of synapses, also occurs physiologically in the

developing brain, and chemicals interfering with this process (which is longer lasting than neuronal loss due to apoptosis) would have the most significant adverse effects on brain functions (Webb et al., 2001). It has become apparent that glial cells (astrocytes, oligodendrocytes and microglia) also play a relevant role in brain development and may be the target of toxic action (Aschner and Costa, 2004), and several chemicals exert profound neurotoxic effects when exposure occurs during the brain growth spurt, characterized by extensive glial cell proliferation and maturation. In addition to all sensitive processes described, the developing brain is distinguished by the absence of a blood-brain barrier. The development of this barrier is a gradual process, beginning *in utero* and reaching completion around postnatal month six in humans (Rodier, 1995). The incomplete development of the blood-brain barrier allows endogenous and exogenous chemicals, normally excluded from the brain, to freely enter the developing brain.

Of the approximately 200 chemicals which have been found to be neurotoxic in humans, a great number are developmental neurotoxicants (Grandjean and Landrigan, 2006). As the developing brain is often more sensitive than the adult brain to toxic insult, neurotoxicity may be observed at lower exposure levels, or be different from those observed in adult, upon similar exposure. In some cases, developmental exposure to neurotoxicants results in morphological alteration of the CNS, with accompanying changes in functions. However, in several instances, functional changes may be the result of more subtle biochemical and molecular alterations without major structural abnormalities. Exposure to chemicals which may adversely affect the nervous system has been suggested to be associated with a number of developmental disabilities (learning disabilities, attention-deficit hyperactivity disorder, dyslexia, sensory deficits, mental retardation, autism spectrum disorders) which are diagnosed in children at an alarmingly increasing rate (Miodovnik, 2011).

4. Neurodevelopmental effects of air pollution: animal studies

The increasing evidence that elevated air pollution may adversely affect the development of the nervous system, and thereby cause significant behavioral deficits in children, has been recently underlined (Kicinski and Nawrot, 2015; D'Angiulli, 2018; Payne-Sturges et al., 2019; Sunyer and Dadvand, 2019). Indeed, epidemiological and animal studies suggest that young individuals may be particularly susceptible to air pollution-induced neurotoxicity (Calderon-Garciduenas et al., 2008, 2011; 2012; Freire et al., 2010; Guxens and Sunyer, 2012; Guxens et al., 2014), with experimental studies supporting observations in humans and *vice versa*. Regarding controlled animal studies, it has been reported that *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 (Yokota et al., 2009, 2013; Suzuki et al., 2010). Early postnatal exposure of mice (PND 4–7 and 10–13) to concentrated ambient PM (308.5 μg/kg) 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, 2014). Additional studies in mice showed that post-natal administration of DE-PM caused changes in GFAP expression in various brain regions (Morris-Schaffer et al., 2019), while a similar exposure to low level ultrafine particles caused male-specific learning and memory dysfunctions (Cory-Slechta et al., 2018). Depression-like responses were found in mice exposed prenatally to urban air nanoparticles (350 μg/m^3) (Davis et al., 2013). Other studies in mice have shown that developmental DE exposure 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, 2009; Tsukue et al., 2009; Win-Shwe et al., 2008, 2014). A recent study in mice (Ehsanifar et al., 2019) reported that pre-natal exposure to DE particles (350 μg/m^3) caused anxiety, spatial memory disorders and altered expression of hippocampal pro-inflammatory cytokines (e.g. IL-6) and NMDA receptor subunit in the hippocampus of adult offspring. Zhang et al. (2018) found that maternal exposure of mice to $PM_{2.5}$ (75–1000 μg/m^3) altered the development of the cerebral cortex and induced significant apoptosis in the offspring. Yet another recent study (Cui et al., 2019) found that pre-natal exposure of mice to $PM_{2.5}$ (400 μg/m^3) enhanced spontaneous locomotion and exploratory behaviors and altered dopamine and glycine pathways in the brain. While all these studies were carried out in mice, evidence of developmental neurotoxicity of air pollution in other animal species also exists. For example, rats were exposed to UFPM during gestation and until 25 weeks of age; male rats exhibited activated microglia, impaired hippocampal neurogenesis, alteration of the blood-brain-barrier, together with behavioral symptoms of depression and deficits in contextual memory (Woodward et al., 2018). In yet another animal species, the rabbit, Bernal-Melendez et al. (2019) found that prenatal exposure to DE (1 mg/m^3) from gestational day 3–27, caused changes in olfactory bulb morphology and in olfactory-based behaviors in the offspring, together with alterations in monoaminergic neurotransmission.

5. Neurodevelopmental effects of air pollution: human studies

Human epidemiological studies support the above experimental findings demonstrating that pre- and/or post-natal exposure to elevated air pollution is associated with behavioral alterations in children (Kicinski and Nawrot, 2015; D'Angiulli, 2018; Payne-Sturges et al., 2019; Sunyer and Dadvand, 2019). Studies in Mexico City have shown elevated levels of neuroinflammatory markers in brains of children exposed to high air pollution, as well as cognitive deficits (Calderon-Garciduenas et al., 2008, 2011; 2013). 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 and incidence of attention deficit hyperactivity disorder (ADHD) (Saez et al., 2018). In contrast, a very large study with eight European population-based birth/child cohorts reported no association between air pollution exposure and ADHD (Forns et al., 2018). 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 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., 2016, 2017), and that the *APOE*ε4 genotype represented a risk factor for some of them (Alemany et al., 2018). In the same population, Rivas et al. (2019) found working memory and attention deficits in boys. 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 et al., 2018).

Altogether, human and animal findings indicate that exposure to air pollution may damage the developing brain and perhaps contribute to neurodevelopmental disorders A major neurodevelopmental disorder is autism spectrum disorder, and as evidence from human epidemiological and from controlled animal studies suggests that air pollution may be associated with its etiology, these studies are discussed in more detail.

6. Developmental exposure to air pollution and 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 et al., 2009). Currently, the term autism spectrum disorder (ASD) is utilized to include autism and a range of similar disorders, such as Asperger's syndrome. The symptoms of ASD are typically present before the age of three, and are often accompanied by abnormalities of cognitive functioning, learning, attention, and

sensory processing. The incidence of ASD appears to have increased in the past few decades, and it is now estimated at about 7–9/1000, though certain studies have identified up to 27/1000 children affected by ASD (Wingate et al., 2012). ASD is more common in males than in females, and represents an important societal problem, as the economic burden of caring for an individual with ASD and intellectual disability during his/her lifespan has been estimated at $2.4 million (Schaafsma and Pfaff, 2014; Buescher et al., 2014). Children diagnosed with ASD present several morphological abnormalities in the brain (Wegiel et al., 2010; Stoner et al., 2014), higher levels of oxidative stress (Frustaci et al., 2012), neuroinflammation and increased systemic inflammation (El-Ansary and Al-Ayadhi, 2012; Depino, 2013).

Susceptibility to ASD is attributable to both genetic and environmental factors (Levy et al., 2009; Landrigan, 2010; Kalkbrenner et al., 2014; Pelch et al., 2019). Though candidate susceptibility genes for ASD have been identified, no single anomaly predominates, and the fraction of ASD attributable to genetic inheritance may be only about 30–50% (Sandin et al., 2014). DNA methylation is also altered in ASD, suggesting that epigenetic dysregulation may contribute to these disorders (Nardone et al., 2014; Ladd-Acosta et al., 2019). Thus, ASD may result from the complex interactions between genes conferring vulnerability and diverse environmental factors. In addition to air pollution (particularly traffic-related), which is discussed in the next section, several other chemicals have been studied in this regard including metals, pesticides and other industrial chemicals (Pelch et al., 2019). A strong association between an environmental factor and ASD has been found with maternal infection (Patterson, 2011). Studies in humans and in various animal species have demonstrated that maternal immune activation (MIA), due to viral or bacterial infection, increases neuroinflammation in the placenta and in the fetal brain, leading to offspring that display ASD-like behaviors (Malkova et al., 2012; Xuan and Hampson, 2014; Estes and McAllister, 2016). Several effects seen in MIA are also found upon developmental exposure to air pollution.

Epidemiological studies have found associations between exposures to traffic-related air pollution and ASD and such findings are supported by a few animal experiments (Costa et al., 2017b). Volk et al. (2011, 2013) and Becerra et al. (2013) found that in California residential proximity to freeways and gestational and early-life exposure to traffic-related air pollution were associated with autism. Another study (Roberts et al., 2013) found that perinatal exposure to DE was significantly associated with ASD, particularly in boys, while two studies in Taiwan and in Pennsylvania, respectively, reported an increased risk of ASD associated with PM (Jung et al., 2013; Talbott et al., 2015). A similar study in two cohorts (North Carolina and California) also reported an association between PM exposure and ASD, particularly when exposure occurred in the third trimester of pregnancy (Kalkbrenner et al., 2015). The latter finding was also reported by Raz et al. (2015) in the Nurses' Health Study II cohort. Additional studies population-based in Vancouver, British Columbia (Pagalan et al., 2019) and in Cincinnati, OH (Kaufman et al., 2019) reported an association between exposure to nitric oxide and ASD, and between ozone and $PM_{2.5}$ and ASD, respectively. A recent study in Shanghai, China found that exposure to $PM_{2.5}$, and PM_{10} during the first three years of life significantly increased the risk of ASD (Chen et al., 2019). Similarly, a study in Denmark reported an association between postnatal exposure to air pollution (particularly $PM_{2.5}$ and sulfur dioxide) and ASD (Ritz et al., 2019).

Though these epidemiological studies show moderate to strong associations between exposure to air pollution *in utero* and/or early in life and risk of ASD, they have been criticized because of the exposure matrix and multiple confounding factors (Fordyce et al., 2018). However, animal studies generally agree with the positive human observations (Costa et al., 2014, 2017a; 2017b). Developmental exposure of mice to DE is associated with behaviors like those present in humans with ASD, including higher motor activity, increased self-grooming, and rearing (Thirtamara Rajamani et al., 2013). Postnatal exposure to concentrated ambient ultrafine particles (on PND 4–7 and 10–13) caused persistent glial cell activation, ventriculomegaly (lateral ventricular dilation), and changes in cytokines and neurotransmitters which occurred preferentially in male mice (Allen et al., 2014). These investigators also reported male-specific alterations in social novelty preferences (an indication of low sociability) and a reduction in testosterone levels (Sobolewski et al., 2018). In another study, prenatal exposure to UFPM was found to cause hypermyelination of the cerebellum in male mice only, together with ultrastructural abnormalities and increase in iron content (Klocke et al., 2018), as also seen in ASD (Fatemi et al., 2012). Chang et al. (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). Similarly, Church et al. (2018) found that exposure of mice to $PM_{2.5}$ (138 μg/m^3) throughout gestation and until PND 10, decreased sociability, reduced social interactions, and increased grooming behavior, particularly in males. Chang et al. (2019) also reported neuroinflammation (increase in IL-6) and reduced expression of reelin in the cerebral cortex of DE-exposed mice, together with subtle alterations in cortical layering, as also found in ASD (Stoner et al., 2014). A study in rats also reported that postnatal exposure to $PM_{2.5}$ caused communication deficits, poor social interactions, and novelty avoidance, together with microglia activation and increases in pro-inflammatory cytokines (Li et al., 2018). 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 also seen in ASD.

7. Mechanistic considerations of air pollution-induced developmental neurotoxicity

Oxidative stress and inflammation are believed to the most important contributors to the adverse effects of air pollution on the respiratory and cardiovascular systems (Møller et al., 2014). While the precise mechanisms or air pollution developmental neurotoxicity are still elusive, oxidative stress and neuroinflammation appear to play important roles. Indeed, the fact that air pollution causes systemic inflammation, microglia activation, oxidative stress, and neuro-inflammation provides biological plausibility and potential underlying mechanisms for the observed association between exposures and ensuing risk of neurodegenerative and neurodevelopmental diseases (Kraft and Harry, 2011). Such oxidative and neuroinflammatory processes may be caused *in situ*, for example by PM that find access to the brain, but the potential contribution of peripheral inflammation to neuro-inflammation should also be considered (Hopkins, 2007; Mumaw et al., 2006). In the CNS, activation of microglia causes an increase in oxidative stress and in pro-inflammatory cytokines. Oxidative stress and neuroinflammation are believed to play a role in PD (Qian et al., 2010; Hirsch et al., 2012) and in AD (Heneka et al., 2015; Huang et al., 2016) pathogenesis. Additional mechanisms (e.g. impairment of adult neurogenesis, alterations of microRNAs, changes in excitatory or inhibitory neurotransmission) potentially involved in air pollution-associated neurodegeneration are discussed by Costa (2017).

Activation of microglia and subsequent oxidative stress and neuroinflammation caused by air pollution may also explain the effects seen following developmental air pollution exposure. For example, microglia-generated pro-inflammatory cytokines could lead to the observed hypomyelination and ventriculomegaly via toxicity to oligodendrocytes (Allen et al., 2017). Microglia activation and neuroinflammation may also play a role in the ASD-like effects observed in mice developmentally exposed to DE (Chang et al., 2018, 2019); an initial increase in IL-6 would lead to an epigenetic-mediated decrease in

reelin expression causing alterations in cortical layering (Chang et al., 2019).

8. Conclusions and future perspectives

During the past several years evidence has been accumulating providing strong support to the fact that high level of air pollution may be associated with neurotoxicity. Epidemiological studies in human populations and experimental studies in animals, as well as *in vitro* observations, provide substantial evidence of the ability of air pollution to adversely affect the CNS (Costa et al., 2014, 2017). Of note is the fact that age appears to represent a significant susceptibility factor, with the very young and the elderly being more affected, and there is increasing evidence that air pollution may play an etiological role in neurodevelopmental diseases and in neurodegenerative disorders. Regarding the former, most attention has been given to the association of air pollution with ASD, observed in humans and supported by animal studies. However, one should also consider other developmental disorders such as attention deficit hyperactivity disorder or early onset schizophrenia.

Several questions remain to further our understanding of the effects of air pollution on the developing brain. For example, epidemiological studies are not always consistent regarding which component(s) of air pollution may be more strongly associated with a certain outcome. Additionally, it would be important to carry out studies in population with chronic high-level air pollution, such as in certain urban areas of India or China. A better understanding of the cellular and molecular mechanisms responsible for the developmental effects of air pollution is also needed, as it may lead to specific therapeutic interventions (targeting, for example, microglia activation). Additional important issue would be those of potential gender differences in susceptibility and of possible gene-environment interactions. Furthermore, longitudinal studies investigating whether developmental exposure to elevated air pollution may lead to accelerated aging or to an increased incidence of neurodegenerative disorders would also be of much interest considering the ever-increasing interest in fetal or early-life origin of diseases. Needless to say, that any effort at diminishing emissions and thereby increasing air quality would be warranted.

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Declaration of competing interest

The authors declare that they have no conflicts of interest.

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