

# Air pollution and your brain: what do you need to know right now

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Research links air pollution mostly to respiratory and cardiovascular disease. The effects of air pollution on the central nervous system (CNS) are not broadly recognized. Urban outdoor pollution is a global public health problem particularly severe in megacities and in underdeveloped countries, but large and small cities in the United States and the United Kingdom are not spared. Fine and ultrafine particulate matter (UFP) defined by aerodynamic diameter (<2.5- $\mu\text{m}$  fine particles,  $\text{PM}_{2.5}$ , and <100-nm UFP) pose a special interest for the brain effects given the capability of very small particles to reach the brain. In adults, ambient pollution is associated to stroke and depression, whereas the emerging picture in children show significant systemic inflammation, immunodysregulation at systemic, intratechal and brain levels, neuroinflammation and brain oxidative stress, along with the main hallmarks of Alzheimer and Parkinson's diseases: hyperphosphorylated tau, amyloid plaques and misfolded  $\alpha$ -synuclein. Animal models exposed to particulate matter components show markers of both neuroinflammation and neurodegeneration. Epidemiological, cognitive, behavioral and mechanistic studies into the association between air pollution exposures and the development of CNS damage particularly in children are of pressing importance for public health and quality of life. Primary health providers have to include a complete prenatal and postnatal environmental and occupational history to indoor and outdoor toxic hazards and measures should be taken to prevent or reduce further exposures.

**Key words:** children; cognition and mood effects; neurodegeneration; neuroinflammation; particulate matter; stroke and depression; urban air pollution

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## Introduction

Millions of people around the world, 74 million in the United States and 24 million people living in the Mexico City Metropolitan Area (MCMA) are

involuntarily inhaling ambient concentrations of particulate matter (PM) above safety standards. In the United States, millions of people in busy corridors from New York–New Jersey–Long Island to relatively small cities like Provo, UT are chronically exposed to fine PM year after year (Chen and Kan, 2008). Well-documented air pollution events have been described in United Kingdom including the 1952 London episode with a high impact on public awareness of pollution (Bell *et al.*, 2004; Beelen *et al.*, 2013; Langrish and

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Mills, 2014). Cohort longitudinal studies across Europe show 7% increase in natural cause mortality with each  $5 \mu\text{g}/\text{m}^3$  in fine  $\text{PM}_{2.5}$  (Beelen *et al.*, 2013; Langrish and Mills, 2014). According to a report by the European Topic Centre on Air and Climate Change (ETC/ACC), fine PM air pollution is associated with 455 000 premature deaths every year in the EU's 27 member states, including 46 200 in the United Kingdom (ETC/ACC, 2009 report). Air pollution levels have been decreasing in developed countries, while in developing countries and countries in transition, the problem is decreasing at a very low rate or even worsening. MCMA is an example of a polluted megacity with over 40 000 industries, >4 million vehicles that consume more than 40 million liters of petroleum fuels per day and produce thousands of tons of pollutants (INE, 2011). Since MCMA lies in an elevated basin 2240 m above sea level, surrounded on three sides by mountain ridges, surface, as well as surface-based air temperature inversions occur frequently, trapping pollutant emissions close to the surface and aggravating the pollution (Bravo-Alvarez and Torres-Jardón, 2002). MCMA geographical setting and the climatological characteristics along with the relatively little mobility of their residents allows for the opportunity of studying health effects associated to sustained yearlong exposures to concentrations of air pollutants above the current US National Ambient Air Quality Standards.

## PM air pollution

Air pollution is a complex mixture of PM, gases, organic and inorganic compounds present in outdoor and indoor air. Urban outdoor pollution is a global public health problem (Molina and Molina, 2004). PM defined by aerodynamic diameter (>2.5 to <10- $\mu\text{m}$  coarse particles,  $\text{PM}_{10}$ , <2.5- $\mu\text{m}$  fine particles,  $\text{PM}_{2.5}$ , and <100-nm ultrafine particulate matter (UFPM)) poses a special interest for the brain effects given the capability of fine and UFPM to reach the brain (Block and Calderón-Garcidueñas, 2009). The major sources of fine and UFPM in the environment, that is, combustion sources from gas, oil, coal, industry and fires, metals and biological materials are common threat in urban and rural sites (Brook *et al.*, 2010). The smaller the particle, the larger the surface area, the

better lung penetration and diffusion and major particle deposition in the respiratory tract and direct translocation into the brain. A significant threat not contemplated by health care workers are man-made particles <100 nm. Nano-sized materials are included in many consumer products and daily use indoor machines produce them in significant amounts, and thus humans are being exposed on daily bases (ie, tooth paste, flavor enhancers, food additives, food and drink containers including baby bottles and pacifiers, laser printers, etc.; Hagens *et al.*, 2007; Benn *et al.*, 2010; Bergin and Witzmann, 2013). Most people spend >90% of their time indoors, so indoor air pollution is very important: smoking, cooking, candle/incense burning, cleaning and use of plastics and conglomerates all contribute to indoor pollution (Habre *et al.*, 2013). Poor air quality in schools and in-vehicle concentrations of pollutants are also of deep concern (Brown *et al.*, 2012; Annesi-Maesano *et al.*, 2013).

As in any city, air quality in MCMA is determined by the balance between pollutant emissions and the capacity of the geographical site to eliminate, disperse or concentrate those air pollutants. Despite MCMA rapid growth and development, air quality has improved during the past two decades. Nevertheless, residents remain exposed to concentrations of airborne pollutants exceeding ambient air quality standards, especially for PM and ozone, the two most important pollutants from the standpoint of public health (Brook *et al.*, 2010). The higher socioeconomic status (SES) MCMA population lives toward the south and west of the urban area with access to vegetation, water and better road networks. The industry is located primarily in the northeast and northwest, whereas the east side has been covered by large housing low SES developments in areas of difficult access and poor services. This distribution of the population, as well as the intensity and type of activities carried out, has great influence on the spatial distribution of emissions. According to the most recent emissions inventory for the MCMA (Secretaría de Medio Ambiente, Gobierno de Distrito Federal (SMA-GDF), 2008), the distribution of  $\text{PM}_{10}$  depends largely on the activity of vehicles on paved and unpaved streets and roads, and in some urban areas of the northwest, these emissions are added with those generated by heavy industries. The fractional composition of  $\text{PM}_{2.5}$  has been dominated by organic and black

carbon, sulfate, nitrate, ammonium and crustal components, with site- and time-dependent variations (Aiken *et al.*, 2009). Particle species are typically categorized as ‘primary’ if they are emitted in the particle phase and ‘secondary’ if their precursors (volatile organic compounds, NO<sub>x</sub>, SO<sub>2</sub>, NH<sub>3</sub> and others) are emitted in the gas-phase and subsequent chemical reactions bring them to the particle phase.

Diesel and gasoline exhausts emissions have been responsible for a significant fraction of the fine particle primary emissions in MCMA (Molina *et al.*, 2010). Polycyclic aromatic hydrocarbons (PAH) are a family of species, some of which are highly mutagenic and carcinogenic, that are generally associated with black carbon as their emissions are largely from combustion sources (Valle-Hernández *et al.*, 2010).

Peak concentrations of PAHs in MCMA are reached during the morning rush hour and are of the order of 120 ngm<sup>-3</sup>, which is significantly higher than in United States (Marr *et al.*, 2004; Molina *et al.*, 2010). High levels of anthropogenic metals including chromium (Cr), zinc (Zn), copper, lead (Pb), antimony, arsenic, tin and barium complete the toxic potential of fine PM (Molina *et al.*, 2010). As expected, these metals exhibit strong temporal variations in concentration and are largely associated with industrial and mobile sources. Elements representing mostly road traffic, that is, Cr, Mn, Zn and Pb, are typically associated with engine emissions and abrasion of tires and brake pads. V and Ni are interpreted as tracers of long-range transport from the use of heavy fuel oil in the north of the basin (Querol *et al.*, 2008). Pb deserves a special mention. Before 1986, Pb was probably the most harmful pollutant in MCMA, associated with the exclusive use of leaded gasoline and resulting in Pb concentrations three times the air quality standard. In response to a very strong social pressure and to a growing international trend to control car emissions with catalytic converters, PEMEX, the federal Mexican oil company, was forced to reduce the gasoline content of tetra-ethyl-lead (Bravo-Alvarez and Torres-Jardón, 2002) resulting in Pb concentrations ~2 µg/m<sup>3</sup> in 1988 and reaching ~0.5 µg/m<sup>3</sup> by 1998. Although Pb is no longer an air pollutant problem, lipopolysaccharides (products of the outer membrane of Gram-negative bacteria) associated with PM, are detected in very high concentrations in southern Mexico City (Rosas-Pérez *et al.*, 2007). The grim scenario for MCMA residents is a sustained exposure to PM<sub>2.5</sub> several hours per day above the

current standards, every year, in such a way that residents are living in a very effective exposure chamber from conception to death. Is this scenario exclusive for Mexico City residents? The answer is no, Salt Lake City, Tacoma, San Francisco Bay, Los Angeles, Fairbanks, London, Greater Manchester and Oxfordshire residents to name a few have similar scenarios, albeit less severe (Bell *et al.*, 2007; Maheswarang *et al.*, 2010; Williams *et al.*, 2011; Beelen *et al.*, 2013; UK Air Data). On the other hand, millions of Shanghai residents are covered with heavy haze substantially increasing cardiovascular, respiratory and cerebrovascular morbidity and mortality (Xu *et al.*, 2013).

### The impact of polluted air on an adult brain

The first important statement to be made is that age and disease status are key factors on the impact of air pollutants. Associations between stroke, ambient pollution and coal fumes were suggested in the 1980s (Knox, 1981; Zhang *et al.*, 1988). Cigarette smoking as a stroke risk factor (and of course an excellent source of large amounts of PM) was published a decade later (Howard *et al.*, 1998). Ischemic stroke mortality and transient ischemic attacks relate to fine and UFPM exposures even at concentrations below the current standards (Hong *et al.*, 2002; Kettunen *et al.*, 2007; Lisabeth *et al.*, 2008; Bedada *et al.*, 2012; Leiva *et al.*, 2013) and very important from the clinical point of view, outdoor air pollution and proximity to high-traffic roadways impact stroke survival (Maheswarang *et al.*, 2010; Wilker *et al.*, 2013). The largest association between PM<sub>2.5</sub> and ischemic stroke risk was seen with stroke due to large-artery atherosclerosis and small-vessel occlusion: diabetic patients are particularly at risk (O’Donnell *et al.*, 2011). Moreover, the associations involve not only urban pollutants but also dust storms and unfortunate events like 9/11 World Trade Center (Yang *et al.*, 2005; Brackbill *et al.*, 2006). Although most of the literature associating stroke with air pollution emphasizes PM, ozone – a key photochemical pollutant affecting our populations in Mexico City, Los Angeles, San Joaquin Valley, Riverside, Sacramento, Baltimore, Dallas, south-east of England, etc. – is also a big player (Parrish, *et al.*, 2011; Carlsen *et al.*, 2013;

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Suissa *et al.*, 2013). Depression and mood disorders have been associated with air pollution. Increases in PM<sub>10</sub>, PM<sub>2.5</sub>, NO<sub>2</sub>, CO, SO<sub>2</sub>, O<sub>3</sub> and biomass burning are associated with depression in the elderly, and emotional symptoms and suicide attempts in younger subjects (Szyszkowicz *et al.*, 2010; Wisnivesky *et al.*, 2011; Banerjee *et al.*, 2012; Lim *et al.*, 2012). Exposure of animal models to ambient PM<sub>2.5</sub> results in depressive responses and increase hippocampal pro-inflammatory cytokines (Fonken *et al.*, 2011), whereas prenatal nano-PM impacts neonatal neurons and adult behavior in mice (Davis *et al.*, 2013).

### The impact of polluted air on a developing brain

Clean air is fundamental for children's health and well-being. Millions of children are showing an array of adverse short- and long-term health outcomes related to air pollution exposures. Widely recognized among pediatric health providers is the impact of intrauterine factors, parent-child interactions, cognitive stimulation, maternal SES during pregnancy and the child's nutrition and exposure to complex learning stimuli, all vital for brain development (Calderón-Garcidueñas and Torres-Jardón, 2012a). However, air pollution brain effects rooted in intrauterine life and childhood are not generally acknowledged. Air pollution is not broadly recognized in the context of children's brain effects including the presence of neuroinflammation, cognitive deficits, structural brain alterations and neuropathological hallmarks of Alzheimer (AD) and Parkinson's diseases (PD) (Calderón-Garcidueñas *et al.*, 2003; 2008a; 2008b; 2008c; 2009; 2010; 2011a; 2011b; 2012a; 2012b; 2012c; 2013a; 2013b).

A coherent pathway linking exposure to air pollution and brain damage starts with a chronic inflammatory process involving the respiratory upper and lower tracts, which result in a systemic inflammatory response with the production of inflammatory mediators capable of reaching the brain (Calderón-Garcidueñas *et al.*, 2003; 2008a; 2008b; 2008c; 2009; 2011a; 2011b; 2012a; 2012b; 2013a; 2013b). Continuous expression of potent inflammatory mediators in the central nervous system (CNS) and the formation of reactive oxygen species are major findings in urban residents

(Block and Calderón-Garcidueñas, 2009). UFPM, particulate matter-associated lipopolysaccharides, and metal uptake could take place through olfactory neurons, cranial nerves such as the trigeminal and vagus, the systemic circulation and macrophage-like cells loaded with PM from the lungs (Calderón-Garcidueñas *et al.*, 2008c; 2012a). Activation of the brain innate immune responses resulting from the interaction between circulating cytokines and constitutively expressed cytokine receptors located in brain endothelial cells is followed by activation of cells involved in adaptive immunity (Lampron *et al.*, 2013). Monocytes are the main innate immune response mediator cells, producing and secreting TNF $\alpha$ , interleukin-1 $\beta$  (IL-1 $\beta$ ) and IL-6, which in turn recruit and increase the activity of other immune cells. Fine and UFPM could serve as the crucial trigger for a chain of events leading to endothelial activation, disruption of blood-brain barrier (BBB), altered response of the innate immune system, production of autoantibodies to cell junction and neural proteins, neuroinflammation and neurodegeneration. These early changes, amenable to intervention and viewed initially as a compensatory phenomenon by some groups including ours (Perry *et al.*, 2002; Castellani *et al.*, 2006; Calderón-Garcidueñas *et al.*, 2012a; 2013a) are likely critical to onset and progression of the neurodegenerative changes and the full clinical picture seen in AD patients (Castellani *et al.*, 2006).

There is growing recognition of the role of systemic and neural inflammation and the interplay between immunity, neurodegeneration and maladaptive activation of innate/adaptive immunity as key pathogenic phenomenon in AD (Blasko *et al.*, 2004; Dik *et al.*, 2005; Finch and Morgan, 2007; Bonotis *et al.*, 2008; Gomez-Ravetti and Moscato, 2008; Cunningham *et al.*, 2009; Keene *et al.*, 2011). Likewise, change in immune status has been suggested as a plausible biological mechanism by which PM could cause adverse health effects (Eikelenboom *et al.*, 2011). PM has the capability of crossing barriers, including the BBB resulting in neuroinflammation and intrinsically disordered neural proteins associated with neurodegenerative diseases (Campbell, 2004; Win-Shwe *et al.*, 2008; Levesque *et al.*, 2011).

The emerging picture reveals highly exposed urban children exhibit significant neuroinflammation and brain oxidative stress (Calderón-Garcidueñas *et al.*, 2008c; 2012a; 2013a; 2013b). In addition, these

children have extensive abnormal white matter blood vessels, perivascular inflammation and a breakdown of the BBB (Calderón-Garcidueñas *et al.*, 2008c). Fine tuning of immune-to-brain communication is crucial to neural networks appropriate functioning, thus our recent finding of autoantibodies to actin and occludin/zonulin in the presence of BBB compromise might represent one more factor contributing to initiation and/or pathogenesis of neurodegenerative changes. Current data support a role for air pollution in CNS damage and urban children shared mechanistic pathways potentially conducting to AD and PD (Calderón-Garcidueñas *et al.*, 2013a).

### The short- and long-term effects of air pollution upon the CNS

We have discussed plausible mechanistic pathways causing CNS effects associated with sustained exposures of ambient pollutants during a lifetime, however, it should be clear that acute, subchronic or chronic exposures to air pollutants all have detrimental CNS effects. An example of acute and subchronic massive exposures was the World Trade Center 9/11-related environmental disaster (Bills *et al.*, 2008; Jordan *et al.*, 2013; Ozbay *et al.*, 2013). Massive exposure to a complex mixture of inhalable fine PM, nanoparticles (NPs) and toxic chemicals, resulted in persistent mental detrimental effects and evolution toward unknown brain health outcomes beyond posttraumatic stress disorder (Bills *et al.*, 2008; Jordan *et al.*, 2013; Ozbay *et al.*, 2013).

The olfactory bulb (OB) pathology needs special attention because large segments of the world population inhale toxic substances on daily basis that have the potential for harming the olfactory system and penetrating the brain via the olfactory epithelium (Calderón-Garcidueñas *et al.*, 2010). The issue is very important in the context of air pollution because olfactory dysfunction is among the earliest 'pre-clinical' features of AD and PD, occurring in ~90% of early onset cases (Wang *et al.*, 2010; Doty, 2012). Early olfactory deficits in MCMA young residents appear to be associated with the presence of  $\beta$ -amyloid,  $\alpha$ -synuclein, PM in glomerular structures and the massive distortion of the OB organization (Calderón-Garcidueñas *et al.*, 2010). The central delayed brainstem auditory evoked

potentials (BAEPs), auditory impairment and vestibular dysfunction in exposed children is likely related to the extensive brainstem inflammation with accumulation of  $\beta$ -amyloid and  $\alpha$ -synuclein in key auditory and vestibular nuclei (Calderón-Garcidueñas *et al.*, 2011). Neurodegenerative changes in the dorsal motor nucleus of the vagus, the nucleus of the solitary tract, arcuate nucleus, raphe midline, and extra-raphé medial and lateral tegmental neurons (Calderón-Garcidueñas *et al.*, 2011) are similar to the PD stages I and II of Braak *et al.* (2004). The brainstem pathology we are observing in highly exposed children has strong links with both AD and PD (Braak *et al.*, 2004; 2011).

Recent studies have reported associations between prenatal and perinatal exposures to air pollutants and autism spectrum disorder (ASD) in children (van den Hazel *et al.*, 2006; Larsson *et al.*, 2009; Herbert, 2010; Volk *et al.*, 2011; 2013; 2014; Becerra *et al.*, 2013; Roberts *et al.*, 2013; Visser *et al.*, 2013). ASD is likely caused by complex interactions between genetic and environmental factors. ASD is associated to air pollution exposures during pregnancy in US cities with significant air pollution from traffic sources (Becerra *et al.*, 2013). Activation of the maternal immune system during pregnancy and abnormal behavioral development in Rhesus monkey offspring brings up key questions regarding the role of air pollution and autism among vulnerable populations (Bauman *et al.*, 2013). To complicate matters for clinicians in real-world settings, the changes in the diagnostic criteria for autism in DSM-5 is causing significant controversies and concerns among health providers without formal training in research instruments and complicated assessment processes (Hazen *et al.*, 2013).

### Reflections from practice

This paper is the product of discussions among the authors, all of us familiar with MCMA air pollution. We are physicians, pathologists, neuropathologists, auditory system experts, toxicologists, psychologists and atmospheric researchers dealing with children, worried parents and school officials, looking at neurodegenerative pathologies in autopsy materials from seemingly healthy children dying in accidents and having significant trouble in explaining parents plausible biological pathways that will solve all their questions. Several concerns have been raised in this

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short review about the influence of air pollutants upon the adult and the developing brain that involve a wide spectrum of pathologies the clinician should take into account for short- and long-term CNS impact.

In adults, it is imperative to take care of chronic diseases that aggravate vascular, metabolic and structural brain changes, while advising the patient about tobacco and cigarette smoking and harmful occupations and hobbies. In children, the cognitive, auditory and vestibular effects have immediate early school negative effects, while the prefrontal lesions and the diffuse cortical neuroinflammation will be reflected in decreased career opportunities, negative social health outcomes, including increases in delinquent or criminal activity and violence and consequently a major negative impact on the economy in which those individuals reside. An issue everybody ignores is that the teens reduced capacity to block impulsive antisocial behavior that accompanies impaired fluid cognition is having a significant impact on society.

Next, we review more in detail the specific air pollution effects of brain impairment on cognition and behavior that support the practical reflections presented in this paper. Table 1 summarizes in schematic form selected studies examining neuro-cognitive/neurophysiological effects of air pollution in children, adolescents and young adult populations. The table shows the populations and the air pollutants studied, the tests and deficits found, other tests used and the city/cities/country where the study took place. In what follows we will be focusing mainly on the available findings concerning MCMA children and mechanistic studies on brain development in animal research literature.

### **Making the links: detrimental brain effects and cognitive/behavioral functions**

As we have already mentioned, depending on the pollutant component, doses, exposure protocol, age and gender, health status, etc., the detrimental effects range from endothelial dysfunction, BBB breakdown, dopaminergic neuronal damage, DNA damage, white matter lesions, neuroinflammation, formation of free radicals and oxidative stress, to the identification of early hallmarks of AD and PD (Campbell *et al.*, 2004; Fonken *et al.*, 2011;

Levesque *et al.*, 2011; Win-Shwe and Fujimaki, 2011; Wu *et al.*, 2011; Brun *et al.*, 2012; Guo *et al.*, 2012; Sharma and Sharma, 2012; Trickler *et al.*, 2012). The chronic effects of PM<sub>2.5</sub> in mice result in spatial learning and memory deficits with neuroinflammation and hippocampal dendritic alterations (Fonken *et al.*, 2011). Metal accumulation is associated with memory dysfunction, especially if the metal is administered during the neonatal period, a clear example being iron loading in rodents resulting in impaired spatial memory and in long-term retention of object recognition deficient memory (Schröder *et al.*, 2013). Equally important in the context of urban environments is the massive exposure to NPs entering the body mostly through inhalation (Win-Shwe *et al.*, 2011; Brun *et al.*, 2012). Gold and silver NPs have an effect on human embryonic neural precursor cell growth, suggesting a negative impact of NPs on the developing CNS (Söderstjerna *et al.*, 2013). Intense oxidative damage and lipid, protein and DNA peroxidation are observed in mice after intranasal administration of TiO<sub>2</sub> NPs (Ze *et al.*, 2014). Ferromagnetic mineral magnetite (Fe(3)O (4)) NPs cause structural changes of microtubule and tau protein, essential in the memory mechanism and memory dysfunction (Dadras *et al.*, 2013). Ozone, the main component of photochemical pollution in urban areas has been shown to alter adult neurogenesis and produce progressive hippocampal neurodegeneration along with memory deficits in rats exposed to low subchronic concentrations (Rivas-Arancibia *et al.*, 2010).

Clinically healthy urban children from MCMA selected by stringent criteria exhibited structural, neurophysiological and cognitive detrimental effects compared with matched SES, gender, age and mother's IQ low pollution exposed children (Calderón-Garcidueñas *et al.*, 2008a; Calderón-Garcidueñas *et al.*, 2011a). The cognitive deficits in MC children matched the magnetic resonance imaging (MRI) volumetric changes in their right parietal and bilateral temporal areas (Calderón-Garcidueñas *et al.*, 2012b). Highly exposed children without white matter hyperintensities (WMH-) displayed the profile of classical pro-inflammatory defensive responses: high IL-12, production of powerful pro-inflammatory cytokines and low concentrations of key cytokines and chemokines associated with neuroprotection. Conversely, children with WMH+ exhibited a response involved in

**Table 1** Selected studies examining neurocognitive/neurophysiological effects of air pollution in children, adolescents and young adult populations. The table shows the populations and the air pollutants studied, the tests and deficits found, other tests used and the city/cities/country where the study took place

Study	Exposed/pollutants measured	Neurobehavioral/neurophysiological tests	Neurocognitive/neurophysiological results	Other tests/laboratory longitudinal follow-up	City, country
Calderón-Garcidueñas <i>et al.</i> (2008a)	73 children 9.85 ± 2.15 years Urban Mexico City atmosphere	WISC-R	Deficits in a combination of fluid and crystallized cognition tasks: object assembly, picture arrangement, digit span, information, arithmetic, mazes, vocabulary	Brain MRI ApoE genotyping Comparative neuropathology Dog brain RT-PCR	Mexico City versus Control City, Mexico
Suglia <i>et al.</i> (2008)	202 children 9.7 ± 1.7 years Black carbon	Wide range assessment of memory and learning Kaufman Brief Intelligence Test	Decreases on the visual subscale and general index Decreases in vocabulary, matrices and composite intelligence quotient scores	na	Boston, MA, USA
Wang <i>et al.</i> (2009)	861 children 8–10 years NO <sub>2</sub> and PM10	Line discrimination (LDT) Visual retention (VRT) Visual simple reaction time, preferred hand (VRT-Prh) Visual simple reaction time, nonpreferred hand (VRT-Nprh) Continuous performance (CPT) Digit erase (DET) Digit symbol (DSB) Pursuit aiming (PAT) Sign register (SRT)	Visual simple reaction time with preferred hand and with nonpreferred hand, continuous performance, digit symbol, pursuit aiming, and sign register	na	Quanzhou, China
Calderón-Garcidueñas <i>et al.</i> (2010)	87 teens, young adults 21.2 ± 2.7 years Urban Mexico City atmosphere	The University of Pennsylvania Smell Identification Test (UPSIT)	Olfaction deficits in 35.5% of Mexico City subjects ApoE 4 carriers failed 10-items related to Alzheimer's disease $P = 0.01$ versus low air pollution controls	Olfactory bulb neuropathology in children and young adults: $\beta$ A 1–42 and $\alpha$ -synuclein immunoreactivity, ultrafine particles and vascular changes ApoE genotyping	Mexico City versus Control City, Mexico
Freire <i>et al.</i> (2010)	210 children from rural and urban areas Five-year-olds NO <sub>2</sub>	McCarthy Scales of Children's Abilities (MSCA)	Decreases in general cognitive scores and in quantitative, working memory and gross motor areas	One-year follow-up from age four years	Granada, Spain
Calderón-Garcidueñas <i>et al.</i> (2011)	51 children 8.0 ± 0.7 years Urban Mexico City atmosphere	Brainstem auditory evoked potentials (BAEPs)	Significant delays in wave III ( $P < 0.0001$ ), and wave V ( $P < 0.0001$ ) in Mexico City versus controls consisting with delayed central conduction time of brainstem neural transmission	Brainstem pathology in nine children aged 13.9 ± 4.0 years Brainstem inflammation and accumulation of $\beta$ A 1–42 and $\alpha$ -synuclein in auditory and vestibular nuclei. $\alpha$ -synuclein in pigmented neurons of the substantia nigrae	Mexico City versus Control City, Mexico
Haynes <i>et al.</i> (2011)	Rate of criminal adjudications/10 000 people/10–19 years	Criminal behavior	Airborne exposure to Mn, Hg and PM are associated with increased risk of criminal activity adjudication	Antisocial behavior Ecological relationship between county-wide reported airborne emissions of air metals, PM and youth adjudicated for criminal activity	Ohio counties, USA

**Table 1** Continued

Study	Exposed/pollutants measured	Neurobehavioral/ neurophysiological tests	Neurocognitive/neurophysiological results	Other tests/laboratory longitudinal follow-up	City, country
Calderón-Garcidueñas <i>et al.</i> (2011)	20 children 6.95 ± 0.67 years Urban Mexico City atmosphere One-year follow-up	WISC-R	Progressive deficits in digit span and vocabulary in Mexico City children versus controls The cognitive deficits in highly exposed children matched the significant differences in white matter volumes involving right parietal and bilateral temporal lobes	Brain MRI	Mexico City versus Control City, Mexico
Clark <i>et al.</i> (2012)	719 children 9–10 years 22 schools around London's Heathrow airport	Suffolk Reading Scale 2 Child Memory Scale The Search and Memory Task Health	Aircraft noise exposure at school was significantly associated with poorer recognition memory, reading comprehension, information recall, and conceptual recall	Parents completed a self-report questionnaire that included questions on sociodemographic factors, as well as questions on the perceived health of their children and psychological distress measured using the parental version of the Strengths and Difficulties Questionnaire	
Calderón-Garcidueñas <i>et al.</i> (2012c)	20 children 6.95 ± 0.67 years Urban Mexico City atmosphere Baseline and one-year follow-up	WISC-R	MC WMH – children displayed classical pro-inflammatory defensive responses versus WMH+ children responses involving resolution of inflammation, immunoregulation, and tissue remodeling. The MC WMH+ group responded to the air pollution-associated brain volumetric alterations with white and gray matter volume increases in temporal, parietal, and frontal regions and better cognitive performance compared to MC WMH –	Brain MRI Measurement of white matter hyperintensities (WMH) Inflammatory mediators	Mexico City versus Control City, Mexico
van Kempen <i>et al.</i> (2012)	553 children 10.5 ± 0.6 years Schiphol-Amsterdam Airport NO <sub>2</sub> exposures	Simple Reaction Time Test (SRTT) Switching Attention Test (SAT) Hand-Eye Coordination Test Symbol Digit Substitution Test (SDST) Digit Memory Span Test (DMST)	Exposure to NO <sub>2</sub> at school was statistically significantly associated with a decrease in the memory span length Statistically significant associations were observed between road and air traffic noise exposure at school and the number of errors made during the 'arrow' and 'switch' conditions of the SAT	na	Amsterdam, The Netherlands

The table shows the populations and the air pollutants studied, the tests and deficits found, other tests used and the city/cities/country where the study took place.



resolution of inflammation, immunoregulation and tissue remodeling. The WMH+ group responded to the air pollution-associated brain volumetric alterations with white and gray matter volume increases in temporal, parietal and frontal regions and better cognitive performance compared with the WMH- group. We conclude that complex modulation of cytokines and chemokines influences children's CNS structural and volumetric responses and cognitive correlates resulting from environmental pollution exposures. Regardless of the presence of prefrontal WMH, MC children performed more poorly across a variety of cognitive tests, compared with control children.

We have identified a number of abnormalities also within the auditory brainstem nuclei in children exposed to severe air pollution. Specifically, we have observed that neuronal cell bodies within the medial superior olive (MSO) are significantly smaller and more round than those in age-matched control brains (Calderón-Garcidueñas *et al.*, 2011b). We interpret this dysmorphology to indicate injury and dysfunction in the MSO. The MSO is the largest nucleus within the human superior olivary complex and has clear roles in localization of sound sources, encoding temporal features of sound and likely plays an important role in brainstem encoding of speech. Incidentally, similar morphological alterations were observed in autistic children (Kulesza and Mangunay, 2008; Kulesza *et al.*, 2011). Confirming brainstem pathology, MCMA children showed clearly abnormal BAEPs with delays in wave III and wave V but no delay in wave I. These findings are consistent with delayed central conduction time of brainstem neural transmission, and increased risk for auditory and vestibular impairment (Calderón-Garcidueñas *et al.*, 2011b). We are assessing the integrity of the auditory system in highly exposed children through a number of noninvasive techniques, such as BAEPs, otoacoustic emissions, speech recognition tasks and listening in background noise.

It is clear that air pollution exposed children experience a chronic, intense state of oxidative stress and exhibit an early brain imbalance in genes involved in inflammation, innate and adaptive immune responses, cell proliferation and apoptosis. Neuroinflammation, endothelial activation and the breakdown of the BBB contribute to cognitive impairment and pathogenesis and pathophysiology of neurodegenerative states (Roher *et al.*, 2012;

Jian *et al.*, 2013). The associations between cognition and urban pollution has been established in cities like Boston, where black carbon – a marker for traffic PM – predicted decreased cognitive function across assessments of verbal and nonverbal intelligence and memory in nine-year-olds (Suglia *et al.*, 2008).

### **A working framework for prevention and intervention**

Although genetic factors play a key role in CNS responses (as evidenced by the acceleration of neurodegenerative pathology in children carrying an APOE 4 allele), studies such the above mentioned ones in Boston and others, sketch a complex scenario where air pollution and SES can influence neural development and cognition, as well as genetics, nutrition, access to a cognitively stimulating environment, thereby influencing and determining mental health, academic achievements and overall life performance (D'Angiulli *et al.*, 2009; Siddique *et al.*, 2011; Calderón-Garcidueñas & Torres-Jardón, 2012a; Becerra *et al.*, 2013).

Thus, identification of children at risk for cognitive deficits, brain structural/volumetric and neurodegenerative accelerating changes should be prioritized in populations exposed to significant concentrations of air pollutants. There is growing public concern about the direct and indirect influences air pollution may have on several developmental outcomes such as school performance, behavioral changes and mood disorders in children and teens. Moreover, childhood aggression and teen delinquency are increasing in megacities, establishing early environmental health risk factors for violence prediction and prevention (Haynes *et al.*, 2011; Liu, 2011) in populations at risk will be absolutely critical. New concerns involve the association between air pollution exposure and increased risk of attention deficit hyperactive disorder (Siddique *et al.*, 2011) and autism (Becerra *et al.*, 2013) in young and older children.

Strong support for the need of neurocognitive screening comes from a growing psychological and epidemiological literature suggesting evidence of suboptimal cognitive functioning across the developmental span in clinically healthy children (Guxens and Sunyer, 2012; Calderón-Garcidueñas

*et al.*, 2012b). Importantly, a significant proportion of urban schools are situated near major traffic-related air pollution sources (Amram *et al.*, 2011; Amato *et al.*, 2014), and cognitive outcomes may be partly associated with air pollution levels around schools (Mohai *et al.*, 2011).

Consistent with these observations, the National Institute of Environmental Health Sciences/National Institute of Health panel on outdoor air pollution indicated cognitive, neuropsychological (and possibly neuroimaging) screening of children as one of the priority target areas for future research advocating a multidisciplinary collaborative approach wherein brain-related cognitive (henceforth, neurocognitive) development testing would have a prominent role (Block *et al.*, 2012).

Hence, the use of standard neurocognitive tasks to screen clinically healthy children in schools or pediatric offices seems not only desirable but also highly beneficial. Because the primary goal would be to identify children at risk, possibly at the largest scale, the first step could be to screen entire schools in different neighborhoods with different air pollutant profiles. Multidisciplinary approaches for early risk identification could include using air pollution databases from available monitoring stations to gather: (1) Air pollutant profiles in selected geographic area; (2) exposures to traffic-related air pollutants at each child's school and current residence with land use regression models that combine a geographic information system with ambient passive monitoring in the target area; (3) cumulative ambient exposures to fine PM<sub>2.5</sub>; (4) robust baseline information on the oxidative potential and metal content of PM found in the targeted regions; (5) cognitive screening first and, when applicable, more elaborate neurocognitive/neurophysiological follow-ups, which could include EEG/ERPs, BAEPs, MRI, fMRI and MRS.

The first goal in targeted areas will be to define the cohorts with the most risk for neurocognitive deficits based on traffic emissions, fixed sources of contaminants, profile of toxic pollutant components (ie, metals) and cumulative concentrations of fine PM. The initial studies should be followed by interventions aimed at breaking the cycle of air pollution, indoor air pollution, tobacco use, high body mass index, low fruit and vegetable intake and physical inactivity. Since health risk factors are more likely to have a toll on low SES children, identification of spatial concentrations of low SES

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**Table 2** Suggested battery of neuropsychological and psychoeducational tests for the initial screening of school-aged children and teens exposed to urban air pollution

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1. Rapid mental health screening tool for pediatric use that includes: education, activities/peers, drugs/alcohol, suicidality, emotions/behavior discharge resources like HEADS-ED (Cappelli *et al.*, 2012)
  2. Test for episodic memory  
Rey Auditory Verbal learning Test (RAVLT): learning, immediate and delayed recall  
Wechsler's Logical Memory (WLM): immediate and delayed recall
  3. Speed/executive functions  
Digit symbol WAIS-R
  4. Visuospatial function  
Rey Complex Figure Test  
Block design WAIS-R
  5. Semantic memory/verbal functions  
Similarities WAIS-R
  6. Verbal working memory/fluency  
Digit Span WAIS-R  
Word fluency (COWA)
- 

pediatric populations at risk, should be prioritized (Forastiere *et al.*, 2007; Ou *et al.*, 2008).

According to the American Neuropsychiatric Association and the Shulman criteria (Malloy *et al.*, 1997; Shulman, 2000), the ideal cognitive screening instrument should (i) be relatively brief to administer; (ii) be easy to score; (iii) well tolerated and accepted by participants, in our cases both child and parent; (iv) test all targeted cognitive domains; (v) be valid and reliable; and (vi) relatively independent of or controlling for age and education.

A possible battery of tests (easily translatable in many languages) for the initial screening of school-aged children is described in Table 2. The measures in this table have reference to previous neuroimaging findings implicating functional, maturational or structural correlates of frontal, parietal and temporal regions and/or neurocognitive tests applied to air pollution studies in children as seen on Table 1. Because several studies link risk of negative effects of air pollution to early development, from infancy to preschool, screening could start in daycare or during transition from kindergarten to first grade, for example using tools such as the Early Development Instrument (D'Angiulli *et al.*, 2009). With advances in wireless neuroimaging technology, neurocognitive screening may even incorporate rapid EEG/ERP recording procedures.

In summary, air pollution effects on the developing brain may vary along a continuum from

minor subclinical deficits in cognitive functioning to significant cognitive deficits that are identified readily by parents and/or teachers. The detrimental effects may also worsen with the age of the child, thus selected neurocognitive tools ought to be useful for longitudinal studies, across educational backgrounds and expecting overlaps in the functional areas and tests affected. Complex cognitive responses that may be affected include attention and short-term memory, information processing speed and executive function, verbal abstraction and visuospatial and motor skills. We should also expect deficits in auditory and vestibular responses and sound localization, along with olfaction deficits. The diffuse nature of the neuroinflammation and the neurodegenerative changes observed in exposed children obligates us not to rely on a single study or measure but rather to employ a weight of evidence approach incorporating current clinical, neurophysiological, radiological and epidemiological research as well as the results of animal exposure studies to single pollutants/mixtures/or pollutant components. Inflammatory biomarkers play a key role in the identification of children with positive volumetric and cognitive responses to their lifelong pollutant exposures (Calderón-Garcidueñas *et al.*, 2012b) and since neuroinflammation/vascular damage/neurodegeneration go hand in hand (Calderón-Garcidueñas *et al.*, 2013a and 2013b), definition of inflammatory/endothelial dysfunction biomarkers establishing an association between brain growth and cognition are urgently needed.

Of course, in light of the findings reviewed in the present paper, a pressing important question that jumps to mind is whether the prevalence of AD/PD is increased in MCMA? Unfortunately we do not have accurate records from health institutions. Mexico health care is covered by both private and government hospitals and institutes and there is no universal statistical information regarding AD and PD prevalence. Empirically, however, neurologists and general practitioners report a significant increase in the number of cases for both neurodegenerative diseases (Victor Esquivel MD, Neurologist, personal communication). Death certificates that would be a source of information, unfortunately fail to list AD or PD in the certificate, basically because families are reluctant to link their patients to a disease with genetic implications, and so only allowed for the writing of acute

causes of death like pneumonia, but not the base disease. Therefore, the answer to the central issue of incidence of AD/PD in MCMA is very much an open empirical question for future research.

Our ultimate goal is to protect exposed children through multidimensional interventions yielding both impact and reach: cognitive (Diamond and Lee, 2011), family participation (Josephson, 2013) and modifiable lifestyle factors such as diet and micronutrient supply (Villarreal-Calderon *et al.*, 2010; Calderón-Garcidueñas *et al.*, 2012c).

Air pollution brain effects on children and teens ought to be key public health targets.

### Key points to remember

- Risk for stroke and depression are associated with common ambient air pollutants, including fine and UFPM and ozone.
- The stroke risk is present even at pollutant concentrations below the current standards, meaning there is a wide spectrum of susceptibility to pollutants likely related to factors such as the presence of chronic diseases, and genetic and nutrition variables.
- Stroke is not a stroke, *specific patient characteristics modify associations between air pollution and ischemic stroke* (Villeneuve *et al.*, 2012).
- Check for factors that will aggravate the neurological/psychiatric effects of air pollution such as diabetes, hypertension, infectious processes, residency in close proximity to a busy road, changes in occupation, etc.
- Keep an eye on the air quality index of your city, record proximity of the patient to high density traffic (Mohai *et al.*, 2011; van Kempen *et al.*, 2012) or fixed sources of pollutants, check for acute events such as forest fires or the arrival of fumes from a distant area (Chen *et al.*, 2013).
- PM occupational exposures and tobacco are to be taken into consideration as important sources of pollutants.
- The patient's occupation and hobbies are important. Is she an outdoor person? Is he protected against toxic substances at work? Is there a significant source of PM or NPs at the office? Where is the patient from? A good clinical history is a must.
- Parents and school officials should be aware of the high pollutant concentrations in their area and keep children indoors.

- Identification of children at risk for cognitive deficits, brain structural/volumetric and neuro-degenerative accelerating changes should be prioritized in populations exposed to significant concentrations of air pollutants.
- Brain damage is cumulative and has deleterious effects on cognitive, emotional and behavioral areas.
- Preventive measures against the harmful effects of environmental pollution should be referred to and applied as early as the conception time.
- Finally, we must consider whether we want to pay the high price that involves ignoring the serious health impacts of environmental pollution.

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## Conflicts of Interest

None.

## Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the institutional guidelines based on the Helsinki Declaration of 1975, as revised in 2008.

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