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A review of epidemiological studies on neuropsychological effects of air pollution

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Summary

The aim of the present review is to provide an update of the epidemiological evidence of the effects of air pollution on neuropsychological development and impairment, as well as of the evidence on individual susceptibility to these effects. Animal studies have shown deposition of ultrafine particles containing metals in olfactory bulb and frontal cortical and subcortical areas, and overexpression of inflammatory responses, white matter lesions and vascular pathology in these areas that could be the basis for functional and structural brain effects. Several observational studies in the general population have observed cognitive deficits and behavioural impairment in children and the elderly. These effects, however, are not conclusive given the limited number of studies, their small size and their methodological constraints.

Key words: *environmental pollution; nitrogen dioxide; hydrocarbons, aromatic; cognition; intelligence; behaviour and behaviour mechanisms; inflammation; oxidative stress; antioxidants*

The brain and the environment

Mental capital, the cognitive and emotional resources, is a life-course function increasing (or developmental phase) during early childhood, that starts to flatten after age 4 up to youth when it reaches a plateau phase until the fourth-fifth decade of life. Afterwards, it starts a small decline that accelerates after the seventh decade [1]. In the growing phase, maturation of the cortex (i.e., wiring: synaptic changes, and axonal myelination) during the first years of life is very intensive, and the frontal cortex is the last to mature [2]. This period of life is considered an important window for brain development, since the brain's plasticity decreases with age, and a long period of vulnerability in the developmental process where susceptibility to environmental insults is elevated [3]. Environmental factors may also play a role in accelerating the decline phase.

Traffic-related air pollution, basically urban outdoor pollution, is a global public health problem. Cardio-respiratory effects and mechanisms have been fully investigated [4–7]. By contrast, the influence of air pollution on the brain is unknown, with only some preliminary evidence [8].

The major suspected culprit of the systemic health effects of traffic air pollution are the ultrafine particles (UFP; i.e., atmospheric particles with aerodynamic diameter of <100 nm) [9]. Particles from vehicle emissions can be divided into primary particles formed in the vehicle and secondary particles formed in the atmosphere after emission. Primary particles are insoluble agglomerates of carbonaceous material which may contain metallic ash and adsorbed or condensed hydrocarbons; secondary particles, volatile and comprised mainly of hydrocarbons, are generally in the nanoparticle size range (below 30 nm) and mostly soluble. Small insoluble particle size allows better penetration and diffusion and major particle deposition in the respiratory tract, translating to a systemic reaction as well as direct translocation in the brain [10]. There is little information on the trend in UFP in European urban atmospheres, but the increased load of diesel vehicles and recent data [11–12] suggest an upward trend. In cities such as Barcelona, traffic is the origin of 90% of the UFP [13].

Particle deposition in the brain

In rats, intratracheal instillation of particles less than 100 nm labeled with radioactivity was subsequently detected in several organs, including the brain [14]. Ultrafine carbon particles [15] and Manganese (Mn) nanoparticles [16] have been found in the olfactory bulb and the cerebrum and cerebellum after inhalation. Another pathway of deposition of particles into the brain suggested particulate matter (PM) >200 nm (TiO2) may be phagocytised by macrophages and dendritic cells which may carry the particles to lymph nodes in the lung or to those closely associated with the lungs [17]. Changes in cytokine expression in brain mice have been directly linked to intranasal exposure to ultrafine carbon [18].

Animal studies in neuroinflammation

Animals exposed to high levels of air pollution, such as fine and ultrafine PM, lipopolysaccharides associated with PM, ozone, and diesel engine exhaust, showed an increase of proinflammatory cytokines in brain tissue [19–23]. Of special interest is the sequence of studies by Calderon-Gacidueñas et al. with dogs exposed to Mexico City air. Healthy dogs younger than 1 year exhibited neuroinflammation along with disruption of the blood–brain-barrier and accumulation of beta amyloid 42 [24] which was also observed in adult dogs [25]. Furthermore, dogs exhibited frontal white matter upregulation of two important inflammatory genes: Cyclooxygenase-2 (COX2) and interleukin-1beta (IL-1β), as well as diffuse vascular changes [19]. Noteworthy also a study on rats showing that levels of the pro-inflammatory cytokines tumor necrosis factor alpha (TNF-α) and interleukin-1alpha (IL-1α) were dependent on the region analysed and increased in the striatum after exposure to diesel exhaust [21]. Recently, Levesque et al. found that rats exposed to diesel exhaust by inhalation had increased levels of IL-6 protein, nitrated proteins, and ionised calcium binding adaprot molecule-1 (IBA-1) protein (microglial marker) in the whole brain, indicating generalised neuroinflammation [22]. Moreover, diesel exhaust increased TNFα, IL-1β, IL-6, macrophage inflammatory protein-1alpha (MIP-1α), receptor for advanced glycation (RAGE), fractalkine, and the IBA-1 microglial marker in most regions tested, showing a greater response in the midbrain.

Human studies in neuroinflammation

Autopsies from children and young adult residents in Mexico City showed a significant upregulation of COX2, IL1β and cluster of differentiation 14 (CD14) in olfactory bulb, frontal cortex, substantia nigrae and vagus nerves, disruption of the blood-brain-barrier, endothelial activation, oxidative stress, and inflammatory cell trafficking [26]. In a second study on autopsies from children and young adults residents in Mexico, UPF were found to accumulate in the respiratory nasal epithelium as well as in olfactory bulb neurons and in the endothelium and basement membranes of olfactory bulb arterioles together with immunoreactivity to beta-amyloid 42 and alpha-synuclein [27].

Epidemiological studies on child neuropsychological development

Currently, there are some epidemiological studies in children that translate for the first time evidence of the neuropsychological developmental hazards of air pollution from animal studies into humans (table 1) [26, 28–38]. All these studies have used well validated and widely used neuropsychological tests in order to assess several cognitive areas including global intelligence quotient (IQ), language development, or executive function, and motor development. These neuropsychological tests were administered in general by trained interviewer or psychologist and recently by computerised testing. Furthermore, behavioural outcomes such as attention-deficit hyperactivity disorder (ADHD) symptoms or autism disorder were assessed by questionnaires reported by the mother/teacher.

The first study assessed the relation between polycyclic aromatic hydrocarbons (PAH) in particulate mode – collected with individual pumps during two consecutive days in a small sample of nonsmoking pregnant women from New York City (USA) – and mental and psychomotor development and behaviour problem measured in the offspring at different ages from 1 to 5 years old [31–32]. They found that a reduced cognitive development emerged at 3 years old, while no association was shown at younger ages. Moreover, no psychomotor development delay or increased behaviour problem was found at any age. A small cohort was set-up in Krakow (Poland) following the same design and measurements for the air pollution exposure during pregnancy [28]. A reduced IQ score was shown at 5 years old. A similar inverse association between PAH exposure and child IQ at 5 years old has been found in these both studies despite the different levels of PAH observed in each study. However, though these studies were adjusted for potential confounders, such as socio-economic conditions, maternal IQ, or internal doses of lead, they were based on a short measurement of the exposure – only two days – and an air pollution biomarker with low specificity, the PAH. The principal source of PAH is tobacco smoke. Though only nonsmoking pregnant women were included and results were adjusted for second-hand smoking exposure or cotinine levels, these design limitations resulted in preliminary research being not very conclusive. Regarding PAH exposure, another study was carried out in Tongliang, Chongquing (China) where a seasonal coal-fired power plant was operating [30, 35]. Two identical small prospective cohorts enrolled nonsmoking pregnant women and their newborn until 2 years old, one before and the other after the shutdown of the coal-burning plant. Prenatal PAH exposure was measured by PAH-DNA adducts in umbilical cord blood. Before the power plant shutdown, decreases in motor and global IQ were associated with increased cord blood levels of PAH-DNA adducts [35]. However, the closure of the power plant was followed by a significant reduction of the mean PAH-DNA adduct levels, a significant improvement of the social developmental quotient, and a non significant association between PAH-DNA adducts

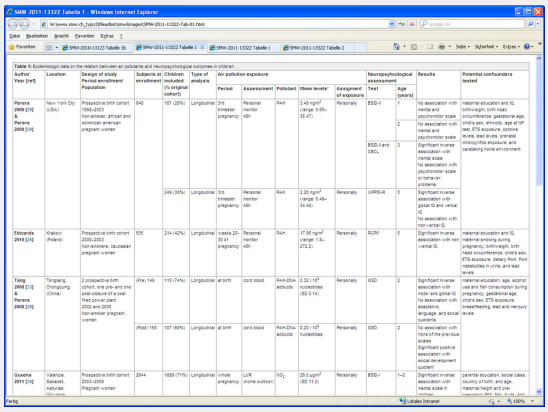

Table 1

Epidemiologic data on the relation between air pollutants and neuropsychological outcomes in children.

and any infant developmental quotients [30]. These studies were the only using biomarkers of exposure, although PAH-DNA is not specific of urban air pollution.

Some other studies have been focused on environmental assessment of more specific markers of traffic-related air pollution using geographic systems such as land use regression modeling based on nitrogen dioxide (NO_2), benzene, black carbon environmental measures and, distance to main road. In the largest study conducted so far, adverse effects of residential NO_2 and benzene exposure during the whole pregnancy – based on land use regression modeling – on infant mental development around 14 months were observed among subjects with low exposure to maternal consumption of fruits and vegetables during pregnancy in 4 Spanish regions [38]. These results were based on a large sample size and were very stable in several sensitivity analyses such as adjusting and stratifying for socioeconomic factors, noise, cord blood lead, indoor air pollution, or smoking exposure. This was the only study that took into account noise exposure as a potential confounder although it was self-reported noise annoyance instead of a direct measure of noise levels. However, children were only 1.5 years old. Another study in a small cohort of children 4 years old carried out in Granada (Spain) assessed the role of residential NO_2 exposure – also based on land use regression modeling – on cognitive and motor development [29]. A nonsignificant reduction of several cognitive subareas was found. A case-control study aimed to examine the association between autism and proximity of residence to freeways and major roadways during pregnancy and near the time of delivery, as a surrogate for air pollution exposure [37]. An increase risk of autism among the 10% of children living within 309 m of a freeway was observed after adjusting for socioeconomic factors and maternal smoking during pregnancy compared to the 50% of children living at a distance higher than 1,419 m. Living near other major roads at birth was not associated with autism. In a birth cohort study carried out in Boston (USA), exposure to black carbon was estimated on the basis of the children's residence – derived by spatial modeling – during the study period where the neurocognitive assessment was done [34]. A significant decrease of global IQ, nonverbal IQ, and visual memory was observed in children around 9 years old, even after adjustment for socioeconomic status, birth weight, tobacco smoke exposure, and blood lead levels.

Some studies have been carried out comparing cognitive and behavioural assessments of children from two areas, one significantly more polluted than the other. A study in Quanzhou, China, compared neurobehavioural performance tests of 431 children from a school in a dense traffic area with 430 children from a school in a clean air area [36]. NO_2, PM less than 10 μm aerodynamic diameter (PM_{10}), and lead were measured by passive samplers in both schools. Only NO_2 concentrations were statistically different between schools. Regarding neurobehavioural outcomes, they found a significant reduction in psychomotor, attention, and sensory scales, although no changes in cognitive function, among children from the school of a dense traffic area compared to children from the school in the clean air area. This study adjusted for a large number of potential confounders including socioeconomic factors, indoor air pollution, and smoking exposure. Calderón-Garcidueñas et al. recruited 55 children from Mexico City with chronically very high concentrations of pollutants and 18 children from Polotitlán, a control city with low levels of pollutants [26]. Results suggested that Mexico City children, but no Polotitlán children, performed significantly behind their normative level of cognitive development, including global IQ, verbal IQ, and several sub-tests of the Wechsler Intelligence Scale for Children-Revised (WISC-R) such as memory or executive function. However, this study did not perform measurement of the exposure and did not adjust for contextual cofactors that differed between the two areas. Similarly another study carried out in India aimed to compare 969 children from Delhi and 850 children from two rural areas of the region of Delhi [33]. Ambient air pollution level was much less in the rural areas due to lesser number of automobiles and air-pollution industries. Prevalence of ADHD symptoms was significantly higher in children of Delhi than those from the two rural areas. Indoor levels of PM_{10} were measured at households and schools of the 60 participants from Delhi and 60 participants from the two rural areas. PM_{10} was found to be positively and strongly associated with ADHD symptoms.

Two ecological studies were carried out in order to assess the association between levels of air pollution around schools and academic performance comparing areas with different air pollution levels, but without any measurement of the exposure. The unit of analyses in these studies were the school [39–40]. Pastor et al. calculated a total respiratory hazard index associated with outdoor air toxics exposures for each public school of California and examined its relationship with the school academic performance index, a summary score of overall school performance [39]. Results indicated that schools located in areas with higher respiratory hazards associated with air toxics also tend to have lower academic performance, even after controlling for a set of school-level variables including student socioeconomic status, teacher quality, parent education, and other factors. Another study set up in Michigan found that schools located in areas with the highest air pollution levels – measured as the distance to major industrial facilities and major highways – had the highest proportions of students who failed to meet state educational testing standards [40]. The analyses were adjusted for school attendance rates, number of students in each school, school expenditures, number of students eligible for the free lunch program, and the racial and ethnic makeup of the school.

Two other studies explored the association between hazardous air pollutants and autism spectrum disorders at 8–9 years, one in the San Francisco Bay area and another in North Carolina and West Virginia following a case-control design [41–42]. Hazardous air pollutants include hundreds of metals, particulate, and volatile organic compounds known to harm human health. The National Air Toxics Assessment (NATA) programme from the US Environmental Protection Agency uses emissions data to model annual-average of hazardous air pollutants levels for each census tract. Individual exposure to hazardous air pollutants was assigned to each subject (cases and controls) using the modelled levels corresponding to the census tract of the

birth address. Windham et al. found a significant association of autism spectrum disorders with higher ambient air concentrations of metals such as cadmium, mercury, and nickel, although results were not adjusted for multiple testing [42]. However, no relationship was shown with aromatic solvents such as benzene, ethyl benzene, styrene, toluene, or xylene neither with PAH or diesel PM. Kalkbrenner et al. estimated null associations between several pollutants including PAH, arsenic, lead, manganese, mercury, and toluene and autism spectrum disorders [41]. The main limitation of this study was the selection of controls that had speech and language impairments. They assume that these problems would not be appreciably affected by air pollution. Nevertheless, as we showed in this review, some studies have pointed out a potential relationship between air pollutants and language development [26, 32].

In related research, early-life exposure to household gas appliances and indoor NO_2 levels was found to be negatively associated with general cognitive functioning and with a higher risk for development of ADHD symptoms at age 4 on 398 preschool children from a birth cohort [43]. Gas appliances produce complex mixtures including NO_2 and UFP. These findings were replicated on four birth cohorts recruited 7 years later though at younger age [44].

Another related research refers to second hand smoking, measured by cotinine levels in children [45–46] and in adults [47] though direct effects of nicotine and cotinine on cognitive impairment and behaviour problems could be the explanation rather than air pollutans.

Overall, these studies open a new horizon for research on the hazards of air pollution for neuropsychological development during childhood, an issue of major worldwide impact.

Epidemiological studies on neuropsychological decline

Few epidemiological studies have assessed the neuropsychological effects of ambient air pollutants in adults (table 2) [48–51]. Chen et al. conducted an analysis using data of the Third National Health and Nutrition Examination Survey (NHANES III) [51]. Individuals were assigned exposure values based on distance between their residence and the monitor. In models adjusted for a large set of variables, increasing levels of estimated annual exposure to ambient ozone prior the examination was associated with a reduced performance in memory and attention tests in adults from 20 to 59 years. However, the association between PM_{10} and cognitive and behavioural outcomes disappeared after adjustment for sociodemographic factors. A study of 399 women aged 68-79 years who lived for more than 20 years in the same residence showed a significant reduction of cognitive function in those of age less than or equal to 74 years that lived within a distance range of 50 m to the next busy road with a traffic density of more than 10,000 cars per day [48]. Nevertheless, no effect in cognitive function was found in relation to PM_{10} levels. Recently, Power et al. reported a significant reduction of cognitive function related to black carbon exposure at residential addresses in a cohort of 680 men aged from 51 to 97 years [49]. Exposure was assessed using land use regression based on black carbon measurements. Results remained similar after adjusting for estimates of lead exposure.

A double blind randomised crossover study was carried out with 10 human volunteers aged from 18 to 39 years [50]. They were exposed to dilute diesel exhaust (300 $\mu g/m^3$) as a model for ambient PM exposure and to filtered air (sham condition) during one hour, separated by a period of two to four days. Crüts et al. showed an increased activity of the left frontal cortex during and after diesel exhaust exposure that indicated a delayed response to diesel exhaust in the frontal cortex.

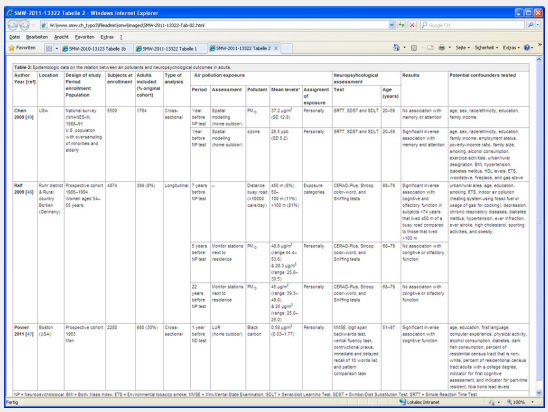

Table 2

Epidemiologic data on the relation between air pollutants and neuropsychological outcomes in adults.

Individual susceptibility to air pollutants

Genome wide studies for ADHD or cognitive function have shown that genetic variants identified explain a small proportion of the phenotypic variability [52–53], indicating the need for new approaches such as incorporating the environmental exposures in the genetic studies.

In a birth cohort study, Morales et al. found a stronger adverse effect of household gas appliances exposure and indoor NO_2 concentrations in children with the *GSTP1* Val-105 allele [43]. In another study, Vrijheid et al. replicated these results showing a reduction of mental development associated with the presence of a gas cooker at home during pregnancy in children with the *GSTP1* Val-105 allele [44]. *GSTP1* protect against oxidative stress and it represents the most strongly expressed glutathione S-transferase isoenzyme in the human brain during early life [54]. Given that *GSTP1* Ile105Val results in a less active enzyme, brain cells from children with the less active *GSTP1* Val-105 variant are more susceptible to biochemical changes induced by early-life air pollution exposure and that modulation in expression levels of antioxidant genes as a result of gene polymorphisms could alter the magnitude of effects caused by UFP.

Another study identified a number of significant interactions between maternal genetic markers and PAH, as well as interactions between newborn genetic markers and PAH, on mental development from 1 to 3 years old before adjusting for multiple comparisons [55]. However, no single marker-PAH interaction remain significant after Bonferroni

correction. Significant interaction effects between haplotypes and PAH were observed in mothers and their newborns after Bonferroni correction, particularly haplotypes of *CYP1A1* and *CYP1B1*. The cytochrome P450 genes *CYP1A1* and *CYP1B1* have been shown to play important roles in the metabolic activation of PAH [54].

High intakes of antioxidant nutrients have been proposed as an important potential modifier of air pollution impairment [58]. Villareal-Calderon et al. found a sustained dorso vagal complex inflammation in mice exposed to Mexico City air, which were mitigated by dark chocolate administration, rich in polyphenols which are potent antioxidants [59]. Regarding other outcomes effects, Jedrychowski et al. reported a non-significant greater reduction of birth weight among those newborns whose mothers reported low fish intake during pregnancy [60]. Within data from the same study, Jedrychowski et al. showed a reduction of the adjusted risk of coughing over the first 2 years of life related with the prenatal exposure to PM less than 2.5 µm aerodynamic diameter ($PM_{2.5}$) in infants whose mothers consumed more fish in pregnancy [61]. Moreover, a protective effect of antioxidant micronutriens such as alpha-tocopherol and carotenoids on the DNA damage associated with prenatal PAH exposure was reported [62].

This research on individual susceptibility will open new fields of knowledge about mechanisms underlying UFP-related neurological effects, as well as identifying susceptible subgroups.

A hypothesis

Based on the above toxicological and epidemiological data the hypothesis that we draw is the following: UFP activates pro-inflammatory genes inducing pro-inflammatory cytokines in human bronchial epithelial cells [63], lung epithelial cells [64], and macrophages [65]. The interaction of macrophages with epithelial cells amplifies cytokine production in those cells, and these cytokines are also present in the blood of subjects during episodes of acute atmospheric air pollution. Furthermore, there is evidence that oxidative stress and induced inflammation translates systemically [66]. Even though most of the available research about inflammatory effects of air pollution refers to the lungs, there is evidence that the oxidative stress and inflammation induced by PM translate systemically beyond the lungs as a result of increased expression of inflammatory genes [9]. For example, elevated particle number counts increased markers of systemic inflammation (IL-6 and fibrinogen peripheral levels) [67], particularly in subgroups with a given genotype [68–69].

UFP are enriched in organic carbon content as well as prooxidative PAH that promote oxidative stress and inflammation. It is not only the particle number concentration, but also particle compositions since different composition may produce different neurological effects. Carbon particles themselves generally adsorb transimetals (including antimony, barium, copper, iron, zinc) emitted from traffic exhaust and also from tire and brake wear. These metals are mainly generated by traffic in current urban atmospheres [70]. Changes in cognitive function in children have been shown to be associated with relatively low internal doses of lead [71] and mercury [72]. In addition to being linked to cognitive deficits in children, lead has been related to a diversity of behavioural problems [73]. Metals have been shown to induce oxidative stress in animal brain [14].

Conclusion and needs

Overall, either deposition of UFP containing metals in olfactory bulb or frontal cortical and subcortical areas, or alternatively the neuroinflammation following the inflammatory systemic responses secondary to oxidative stress triggered by air pollution, could result in white matter lesions and vascular pathology in these areas that could be the basis for the cognitive deficits and behavioural impairment observed in children and elderly. The epidemiological research in the two edges of life (during mental development and during mental decline) is recent and limited and there is need for multicentre and large studies assessing both the growth and the decline of the global mental function, and its specific areas such as memory or executive function, as well as on the clinical impact in social impairment, ADHD, autism or Alzheimer. The potential role of lead and other metals, as well as of noise, as the underlying cause must be ruled out. Furthermore, the epigenetics and the role of the susceptibility genes are a key area of interest.

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