Air Pollution in Brain Development & Aging
Urban Air Pollution

- **Vapor phase**: ozone; NOx & SOx; organics
- **Particulate matter (PM)**:
  fossil fuel combustion from engines & power plants;
  biomass combustion: burning brush & garbage;
  earth crust oxides of aluminum, iron, and silicon

**primary emissions vs secondary aerosols**
(sun-temperature driven chemistry)
Air pollution particulate matter (PM) size classes

- Coarse PM: 2.5 - 10µm
- Fine PM: < 2.5µm
- Ultrafine PM: < 0.25µm
- EPA regulates PM2.5
  USA standard 12.5 µg/m³
- Adult breathing volume
  10 m³ per day
Los Angeles Basin
7 year follow-up on airborne PM2.5µ

carotid thickness increased 4%/10 ug/m³

**Shared inflammatory mechanisms in atherosclerosis and Alzheimer disease?**

<table>
<thead>
<tr>
<th></th>
<th>Atheroma</th>
<th>Senile Plaque</th>
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<tbody>
<tr>
<td><strong>Cells</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macrophages (CD68)</td>
<td>+++ (foam cells)</td>
<td>++ (microglia)</td>
</tr>
<tr>
<td>T helper (Th1)-cells</td>
<td>++</td>
<td>0</td>
</tr>
<tr>
<td>Mast cells, platelets</td>
<td>++</td>
<td>0</td>
</tr>
<tr>
<td>Neovascularization</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td><strong>Proteins</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amyloids</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Abeta</td>
<td>? (platelet APP)</td>
<td>+++</td>
</tr>
<tr>
<td>C-reactive protein (CRP)</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Serum amyloid P (SAP)</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Clotting factors</td>
<td>++</td>
<td>0</td>
</tr>
<tr>
<td>Complement: C3, C5b-9</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Cytokines: IL-1, IL-6</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

CE Finch, Neurobiol Aging, 2005
• PM2.5 & with lower verbal learning ($\beta = -0.32$ per 10 $\mu g/m^3$ PM2.5).
• $\text{NO}_2 > 20$ ppb, lower logical memory.
• $\text{O}_3 > 49$ ppb, lower executive function

Health Retirement Survey (US Sample)
 extremes of PM2.5 differ by 2 y cognitive aging

Jennifer Ailshire, Eileen Crimmins, Am J Epidemiol, 2014
SES and brain sensitivity to air pollution

J Ailshire & A Karraker, submitted

“JC” Jiu-Chiuan Chen, Assoc Prof Preventive Medicine, USC

1. Brain white matter volume loss 5 cm³ per 3.5 μg/m³ PM$_{2.5}$
2. Frontal & temporal lobes and corpus callosum.
3. Equivalent to 1 to 2 years of brain aging in high PM2.5.
Ultrafine PM <0.25u

- ufPM have the highest activity in stimulating cell production of free radicals
- 110 Freeway corridor air is fractionated collect PM0.25
- PM0.25 is trapped on filters and eluted into water suspensions for re-aerosolization. This elution depletes black carbon and water insoluble organics
- Designated as nPM (nano-sized PM)
Re-aerosolized nPM for rodent exposure  
150 hours during 10 weeks

(technology developed by Costas Sioutas, USC)
nPM 150 h activates brain inflammation
Mouse (B6 male)

Morgan et al. *Env Health Pers* 2011
white matter loss

oligodendroglia  microglia

Myelin Basic Protein
Dentate Gyrus- Polymorph Layer

IBA-1 IHC
Dentate Gyrus- Polymorph layer
increased amyloidogenic APP processing

higher βAPPs: αAPPs

Cacciotolo M and Finch CE (unpubl)
Increased brain amyloid EFAD mice with human APOE3 & E4

E4 > E3

Cacciottolo et al in prep.
nPM 150 h alters synaptic proteins:
Decreased hippocampal neurites and glutamate receptors critical for memory
Hypothesis: GluA1 modified by synergies of Abeta-oligomers with nPM

*nPM and ABo both inhibit phosphorylation of GluA1 on Ser831 (conductance, PKC, CamKIIa dependent) and Ser845 (internalization, PKA, calcineurin dependent).

*nPM and ABo both induce NO;
*nPM causes S-nitrosylation
Stroke damage is exacerbated by urban air pollution in a mouse model

William Mack MD,
Assoc Prof Neurosurgery and Neuroscience
Keck School of Medicine, USC

Pre-stroke exposure 3 d/week for 3 weeks (45 hr cumulative). Ipsilateral MCA occlusion after final nPM exposure, submitted
developmental disorders and urban air pollution

Autism spectrum disorders: 2-fold higher from gestation-early childhood near freeway
(Heather Volk, USC)

Childhood obesity: closeness to freeway interacts with tobacco smoke
(Rob McConnell, USC)
Traffic-related air toxics & development in Los Angeles County

• Wilhelm et al 2012, Env Health Persp
  odds of low birth weight increased 5% per quartile of PM2.5 & NOx

• Volk et al 2013, JAMA Psychiatr
  autism 2-fold higher in top quartiles of PM2.5 and NOx
Body mass index (BMI) and childhood exposure to near roadway air pollution (NRP) & tobacco smoke

McConnell R et al, *Env Health Persp*, 2015
Prenatal exposure to nPM alters insulin sensitivity high vs low fat diet (HF vs LF)

Prenatal diesel exposure alters adult brain microglia response to high fat diet with male excess

Bilbo, Duke: Bolton *Brain, Behav, Immune* 2014
Improving LA Air Quality and Lung Development in Children since 1995