16th ETH-Conference on Combustion Generated Nanoparticles
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Paper/Poster-Abstract Form

Name of Author: Roel P.F. Schins
Co-Authors: M. Hullmann, C. Albrecht, D. van Berlo, M.E. Gerlofs-Nijland, A. Hillmann, A.J.F. Boere, P.H.B. Fokkens, S. Weggen, T.A. Bayer, J. Krutmann, F.R. Cassee
Affiliation: IUF – Leibniz Research for Environmental Medicine
Mailing address: Auf'm Hennekamp 50, 40225 Dusseldorf, Germany
Phone / Fax: +49-211-3389269/-3389331 E-mail: roel.schins@uni-duesseldorf.de

Title:
Effects of subchronic inhalation exposure to diesel engine exhaust in the 5xFAD mouse model of Alzheimer's Disease.

Abstract: (min. 300 – max. 500 words)

The abstracts for papers and posters must contain unpublished information on your research subject: background, investigation methods, results and conclusions. Graphs and references are very welcome. Acronyms should be avoided. Abstracts with < 300 words can not be considered. General information on products which are already commercially available can not be accepted as presentations for the conference but are very welcome at the exhibition of particle filter systems and nanoparticle measurement instruments.

M. Hullmann[1], C. Albrecht[1], D. van Berlo[1], M.E. Gerlofs-Nijland[2], A. Hillmann[3], A.J.F. Boere[2], P.H.B. Fokkens[2], S. Weggen[4], T.A. Bayer[3], J. Krutmann[1], F.R. Cassee[2], R.P.F. Schins[1].

[1]IUF – Leibniz Research Institute for Environmental Medicine, Düsseldorf, Germany; [2]National Institute for Public Health and the Environment (RIVM), Bilthoven, Netherlands; [3]Department of Psychiatry, University Medicine Göttingen, Göttingen, Germany; [4]Department of Neuropathology, Heinrich Heine University, Düsseldorf, Germany.

In recent years, it has been suggested that nanoparticles generated from combustion processes, may contribute to the pathogenesis of neurodegenerative diseases such as Alzheimer's disease (AD). We could previously demonstrate that a single, short-term inhalation exposure to diesel engine exhaust (DEE) triggers rapid region-specific gene expression changes in rat brain to an extent comparable to those observed in the lung. The aim of our present study was to investigate the effects of a subchronic exposure to DEE in 5xFAD transgenic mice. This mouse model is characterized by the development of histological, neurological as well as functional impairments which are considered to mimic the development and progression of AD in humans.

Ten weeks old female 5xFAD mice and their non-transgenic littermates were exposed by whole body inhalation to diluted DEE (~1 mg particles/m^3) or clean air for 3 or 13 weeks, during 5 days/week and 6 hour/day. At the end of the exposures, all mice were subjected to a series of behavioural tests (e.g. Y-maze, cross-maze, string suspension). At ten days post-exposure, histopathological, biochemical and molecular-biological changes were evaluated in the lungs and brain tissues of the animals.

In line with the expectations, the 5xFAD mice displayed typically age-dependent behavioural deficits and amyloid plaque formation in cortex and hippocampus. A significant DEE exposure-related effect was observed for the string suspension test, representing a measure of motor coordination/grip strength. DEE exposure was also associated with mRNA expression changes of markers of inflammation and oxidative stress in specific brain regions, including the olfactory bulb. Whole brain tissue homogenate levels of Abeta42 protein were found to markedly increased in the 3 weeks DEE

exposed 5xFAD mice in comparison to the sham exposed littermates. After 13 weeks, further increases in whole brain Abeta42 levels were observed in the transgenic animals, but differences between the DEE and clean air exposed animal were absent at this time point. Quantitative histopathology of plaque-load in cortex and hippocampus of all animals is ongoing.

Our current findings support that the central nervous system may be a sensitive target for combustion-derived nanoparticles. Further research is needed to evaluate the impact of long-term low-level exposure on the development and progression of neurodegenerative diseases in humans.

This work is supported by funds from the Research Committee of the Medical Faculty of the University of Düsseldorf (9772-365), the DFG Graduate School GRK1033 and the RIVM - Centre for Environmental Health, Bilthoven, Netherlands.

Short CV: Dr. Roel Schins is a research group leader at the IUF Leibniz Research Institute for Environmental Medicine, Düsseldorf, Germany. As a trained toxicologist, his longstanding research interest is to unravel mechanisms whereby particles may cause diseases in humans. His current research focuses on the investigation of nanoparticle effects in the lung, the gastrointestinal tract and the brain. Dr. Schins studied Health Sciences at Maastricht University in The Netherlands and worked as a Postdoctoral Research Fellow in the Biomedicine Research Group at Edinburgh Napier University, UK. He is deputy editor of Particle and Fibre Toxicology and has served as expert on the toxicology of (nano)particles to various organisations and bodies including IARC/WHO, OECD, ECETOC, DFG, and DG-SANCO.

Return by e-mail latest 14th of April 2012 to ttm.a.mayer@bluewin.ch

Effects of Subchronic Inhalation Exposure to Diesel Engine Exhaust in the 5xFAD Mouse Model of Alzheimer's Disease

Roel Schins[1], Maja Hullmann[1], Catrin Albrecht[1], Damien Van Berlo[1], Miriam Gerlofs-Nijland[2], Antje Hillmann[3], John Boere[2], Paul Fokkens[2], Sascha Weggen[4], Thomas Bayer[2], Jean Krutmann[1], Flemming Cassee[2]

[1] IUF - Leibniz Research Institute for Environmental Medicine, Dusseldorf, Germany,
[2] National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands,
[3] Department of Psychiatry, University of Medicine, Goettingen, Germany,
[4] Department of Neuropathology, Heinrich Heine University Dusseldorf, Germany

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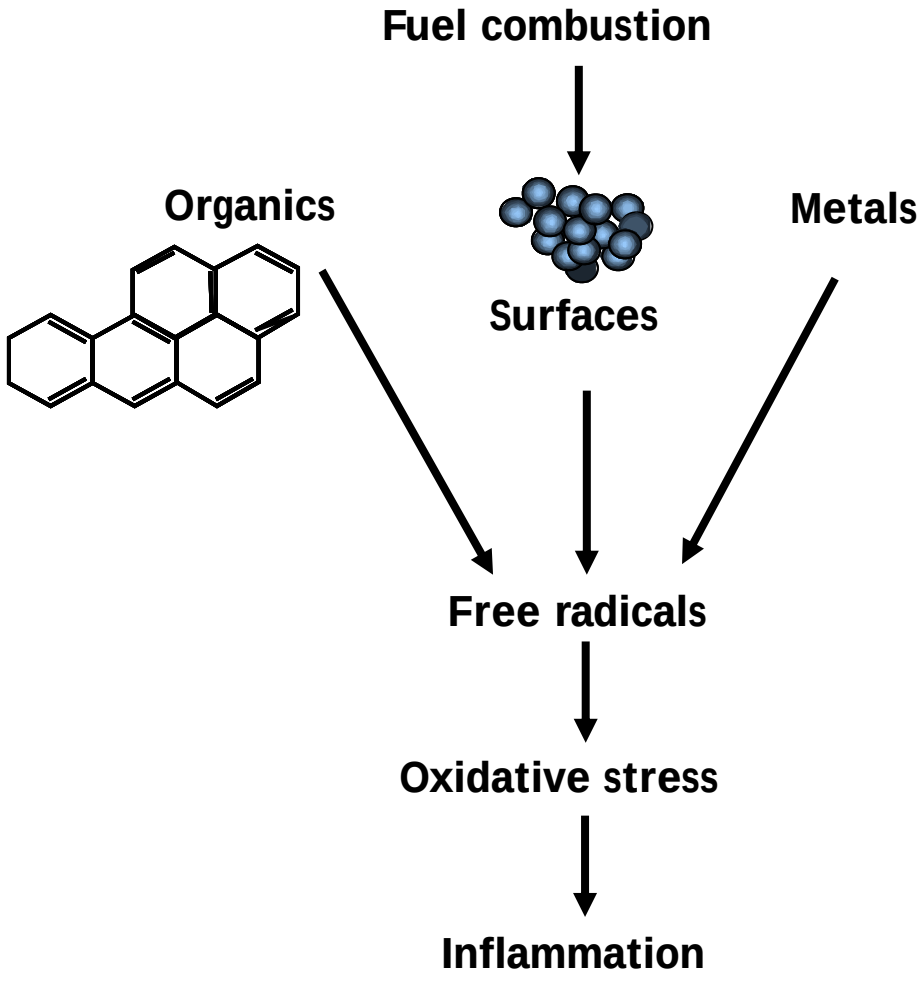
Leibniz Gemeinschaft

roel.schins@uni-duesseldorf.de

Oxidative stress and inflammation caused by combustion-derived nanoparticles



Adverse pulmonary effects, cardiovascular effects, …?

Donaldson et al 2005, *Particle and Fibre Toxicology*

Effects of air pollution particles on the brain

Observations in human studies (histopathology, cognition)

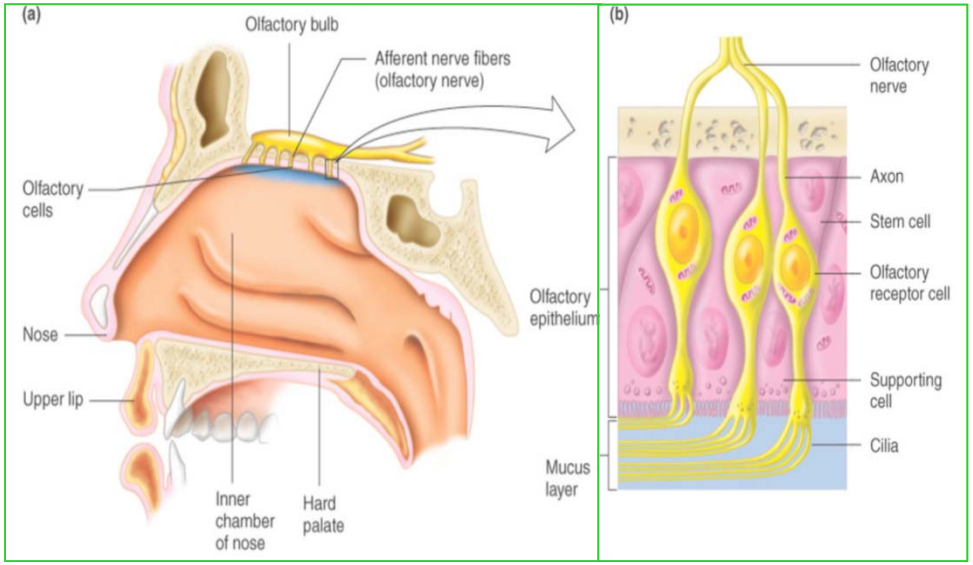
(e.g. Calderon-Garciduenas et al Toxicol Pathol 2004, Brain Cogn 2008; Suglia et al. Am J Epidemiol 2008; Freire et al., J Epidemiol Community Health 2008; Ranft et al Environ Res 2009; Power et al. EHP 2011)

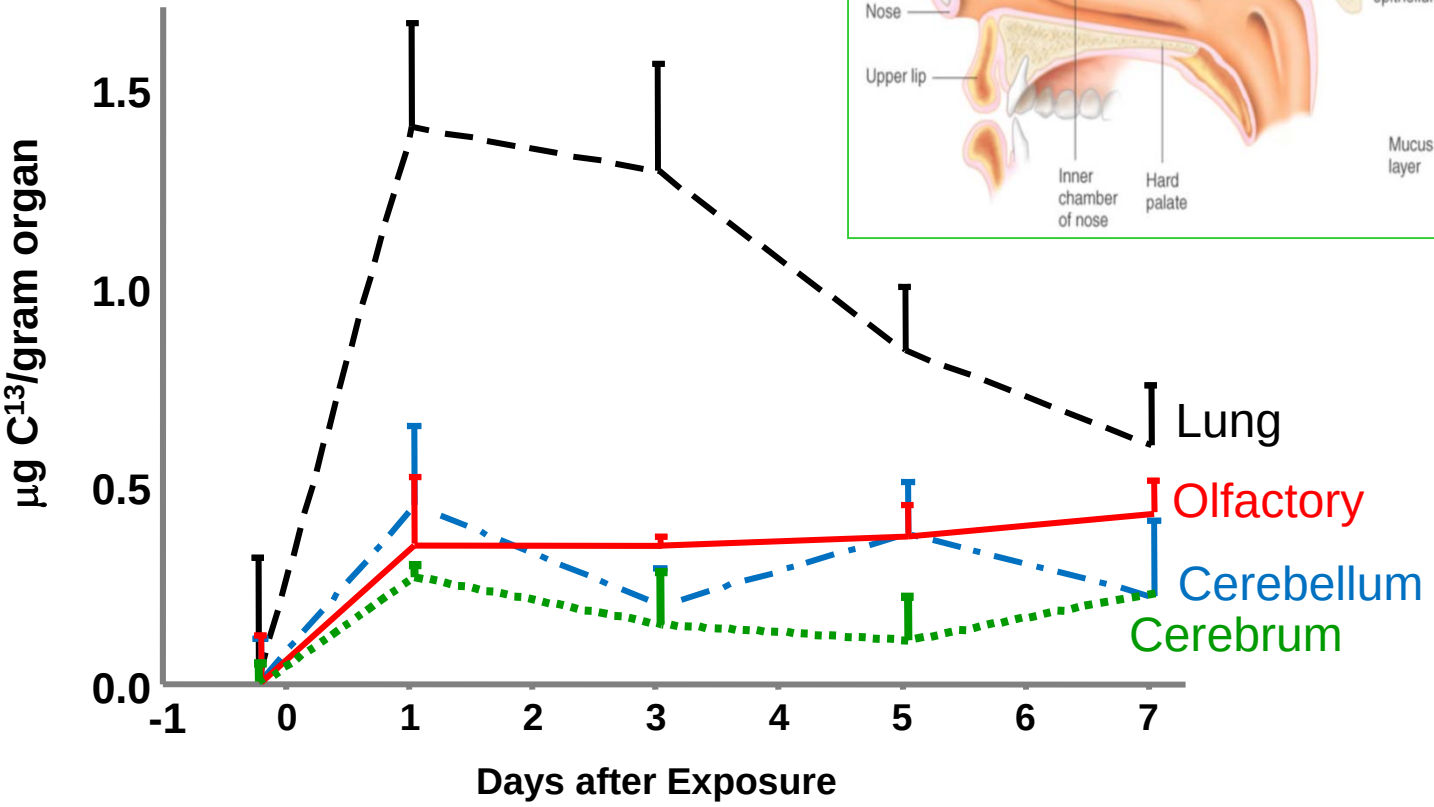
Observations in brains of rodents after controlled exposures to e.g. PM, CAPs, diesel exhaust particles, etc.

(e.g. Campbell *et al.* Neurotoxicol 2005; Kleinman e*t al.* Toxicol Lett 2005; Elder *et al.* EHP 2006; Van Gerlofs-Nijland *et al.* Part Fibre Toxicol 2010; Zanchi *et al.* Inhal Toxicol 2010; Levesque *et al.* EHP 2012)

Carbon nanoparticles translocate to rat brain

Oberdörster et al, 2004 *Inhal Toxicol*





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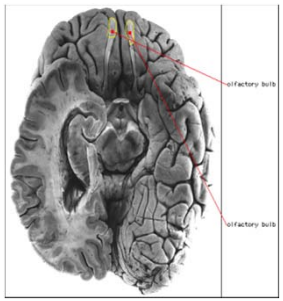
Inhalation of Nanoparticles (<100nm)



BRAIN

TRANSLOCATION

Nasal deposition

olfactory route

Inflammation

Oxidative stress

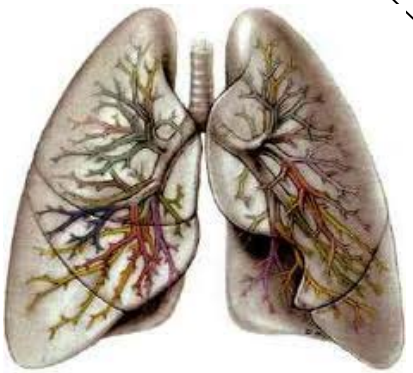
Neurodegeneration

Alveolar deposition

air-blood barrier

Blood

blood-brain barrier



Pulmonary / Systemic inflammation

Van Berlo et al *EXS 2012*

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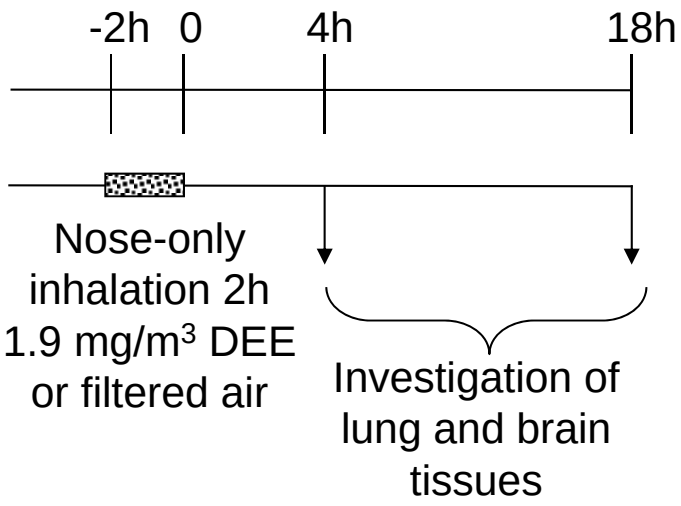
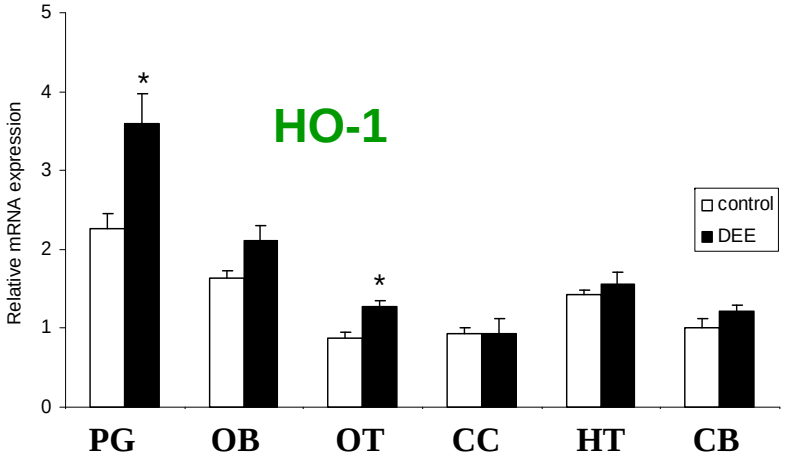
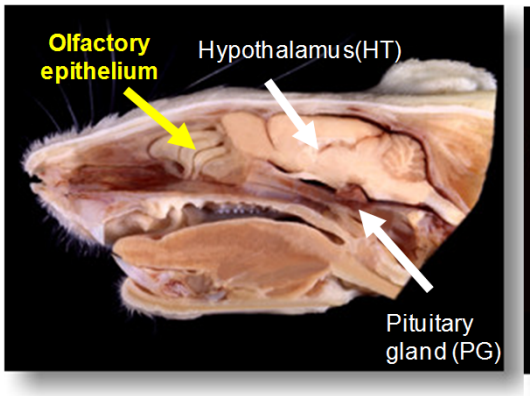
Comparative evaluation of the effects of short-term inhalation exposure to diesel engine exhaust on rat lung and brain

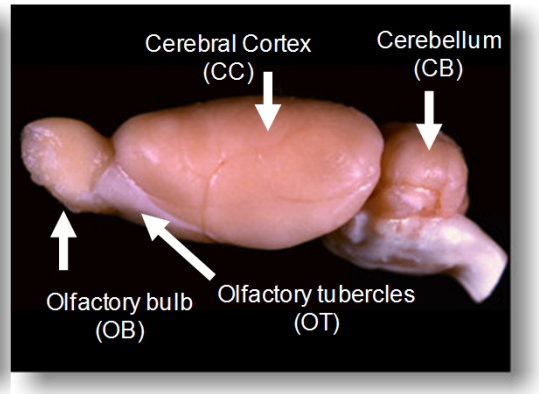
Damien van Berlo[1], Catrin Albrecht[1], Ad M. Knaapen[2,*], Flemming R. Cassee[3], Miriam E. Gerlofs-Nijland[3], Ingeborg M. Kooter[3,**], Nicola Palomero-Gallagher[4], Hans-Jürgen Bidmon[5], Frederik-Jan van Schooten[2], Jean Krutmann[1], Roel P.F. Schins[1].

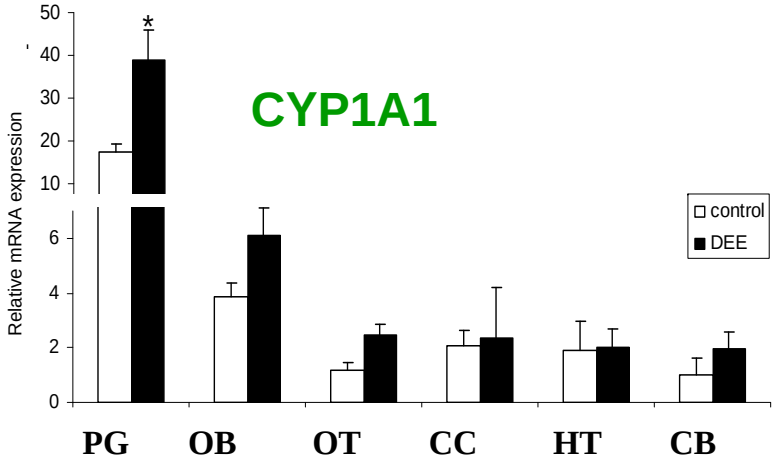
Arch Toxicol 2010; 84: 553-562.





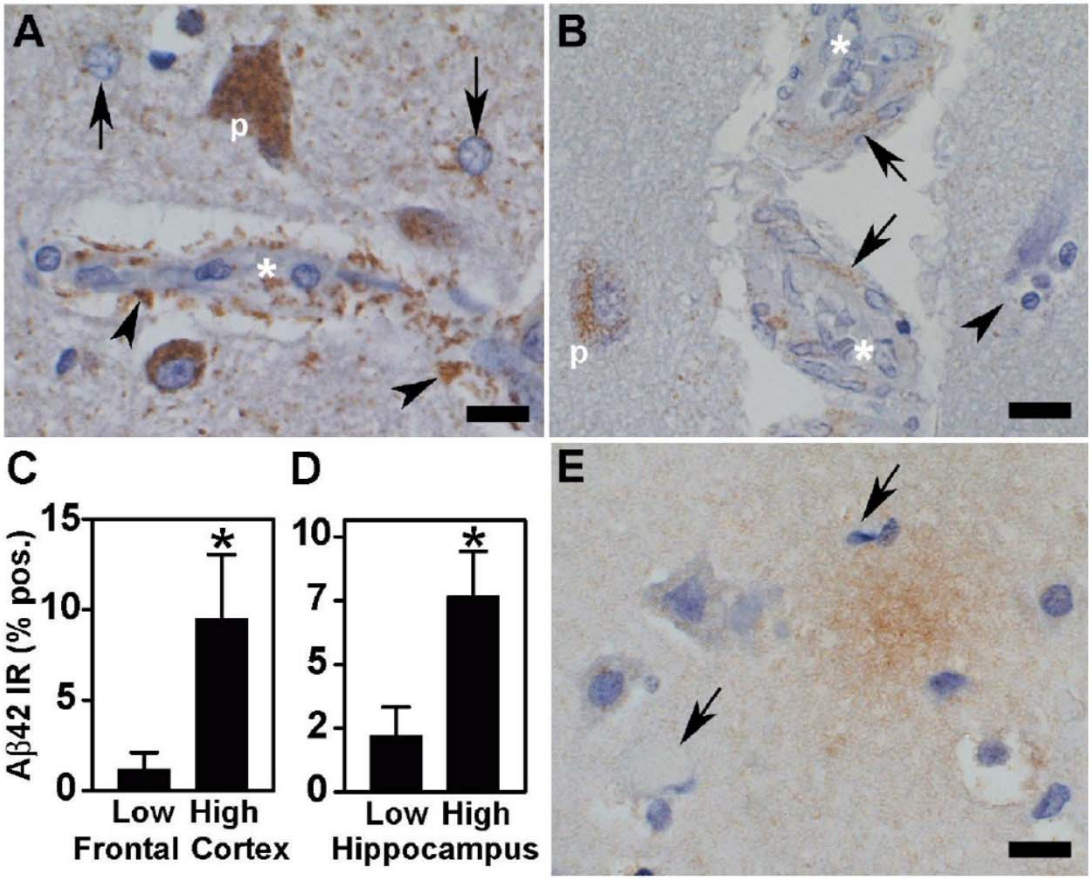






BRAIN INFLAMMATION AND ALZHEIMER'S-LIKE PATHOLOGY IN INDIVIDUALS EXPOSED TO SEVERE AIR POLLUTION

Calderón-Garcidueñas L, Reed W, Maronpot RR, Henríquez-Roldán C, Delgado-Chavez R, Calderón-Garcidueñas A, Dragustinovis I, Franco-Lira M, Aragón-Flores M, Solt AC, Altenburg M, Torres-Jardón R, Swenberg JA. ***Toxicol Pathol 2004;32:650-658.***



Amyloid ß deposition (formation of plaques) & Neuronal degradation

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Environmental Research 109 (2009) 1004–1011

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Long-term exposure to traffic-related particulate matter impairs cognitive function in the elderly ☆

Ulrich Ranft *, Tamara Schikowski, Dorothee Sugiri, Jean Krutmann, Ursula Krämer

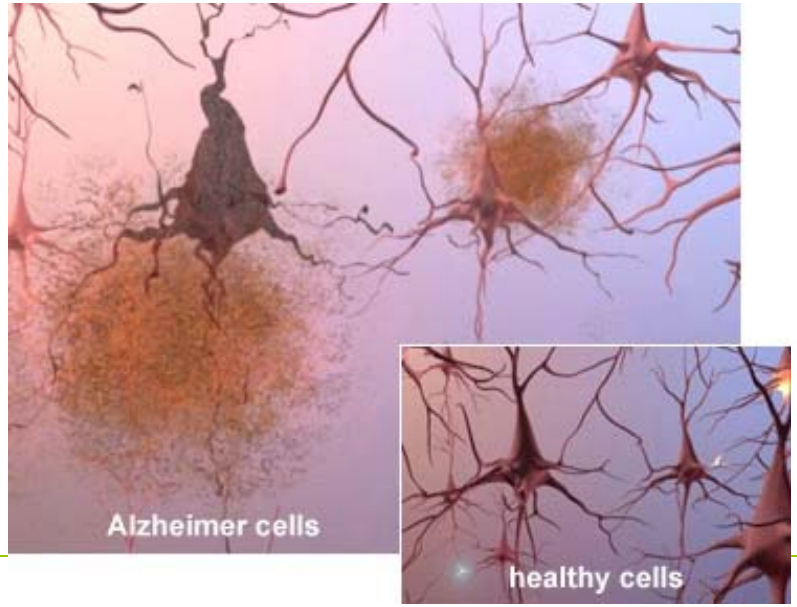
Institut für Umweltmedizinische Forschung (IUF) an der Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Auf'm Hennekamp 50, 40225 Düsseldorf, Germany

Alzheimer´s Disease

- Progressive and fatal brain disorder named after the German neuropathologist *Alois Alzheimer*
- Most common form of dementia
- 27 million people are affected worldwide

→predicted to nearly double every 20 years
(2009 Word Alzheimer Report)

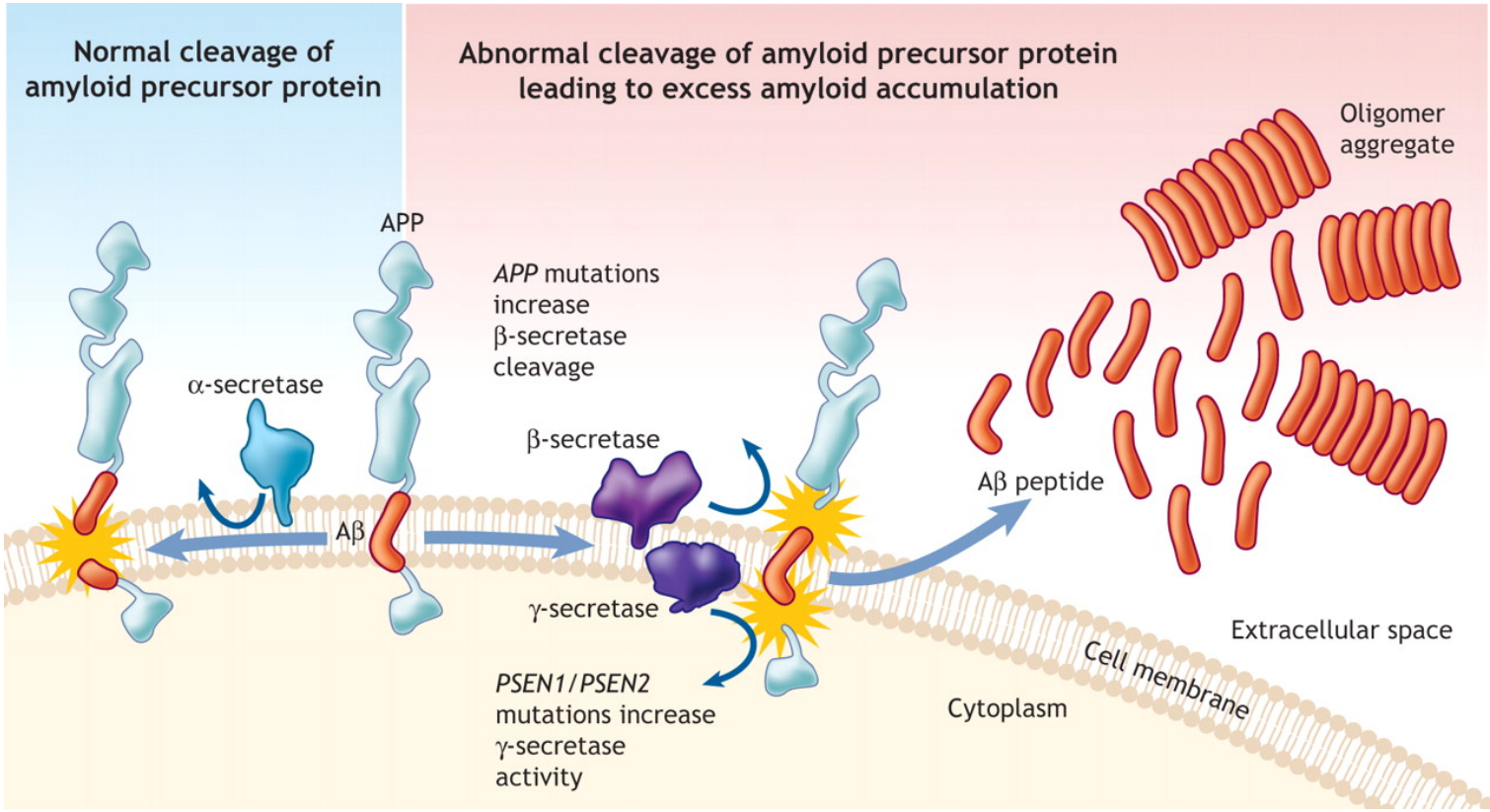
→ Familial Alzheimer's Disease (FAD), approx 0.1 *%*



Formation of plaques and neurofibrillary tangles (Amyloid ß and Tau proteins)

Role of oxidative stress and inflammation

Amyloid-Precursor-Protein (APP) metabolism



Patterson C et al. CMAJ 2008;178:548-556

Alzheimer Model (5xFAD mice)

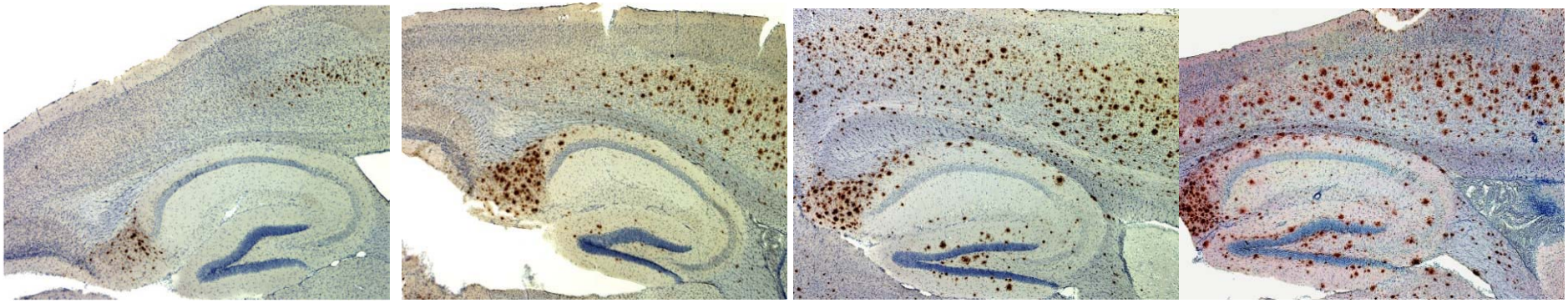
→ mutant human Aß precursor protein (APP) cDNA sequence:

APP K670N/M671L (Swedish) + I716V (Florida) + V717I (London)

→ mutant human presenilin 1 (PS1) cDNA sequence:

PS1 M146L + L286V

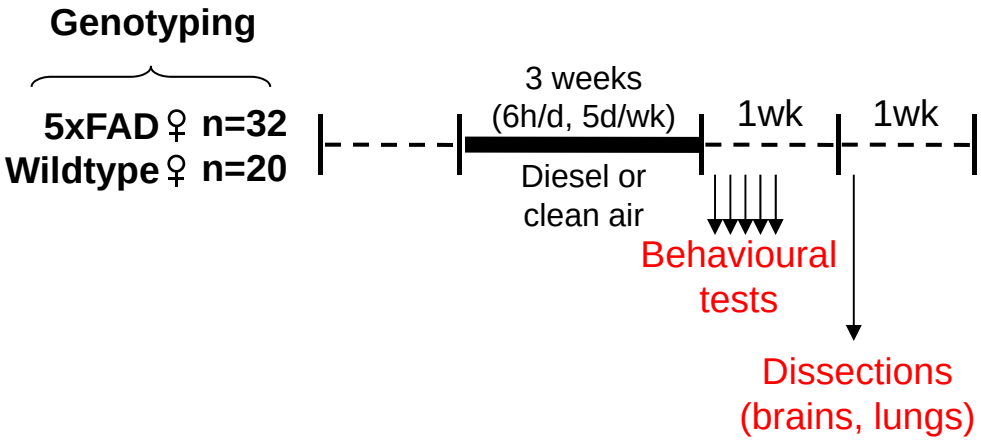
Expression of both transgenes is regulated by neural-specific elements of the mouse Thy1 promoter to drive over-expression in the brain.



Age: 2 months 4 months 6 months 9 months

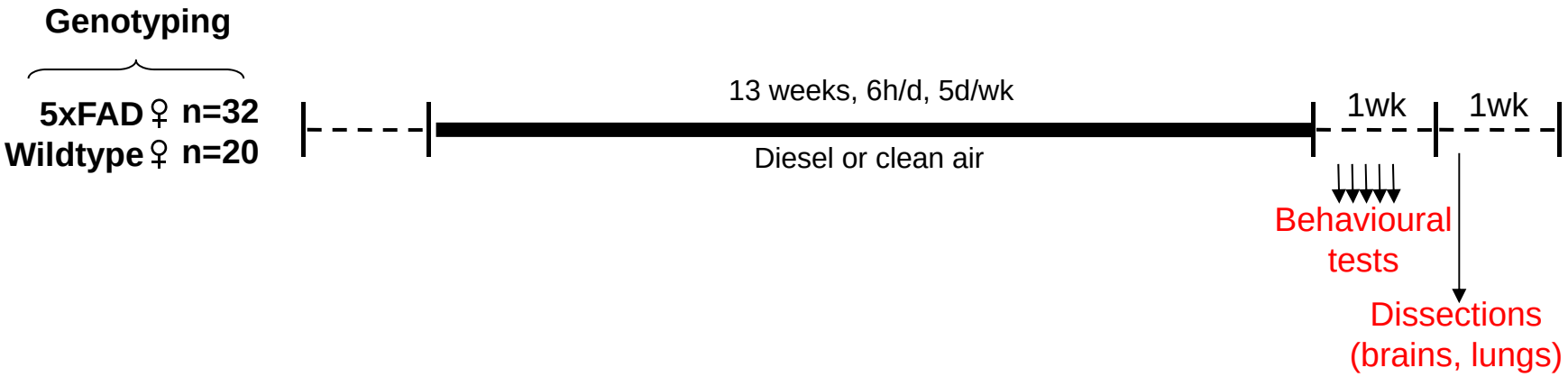
Oakley et al, 2006 *J. Neurosci.*

Study design



Whole body exposure

Mass dose: ~1 mg/m³
Number dose: 2·10⁶ particles/cm³
Mean size: 81 nm (GSD 1.75)



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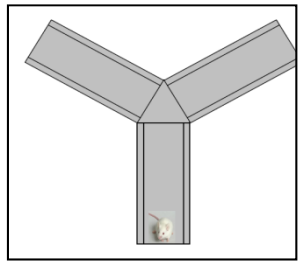
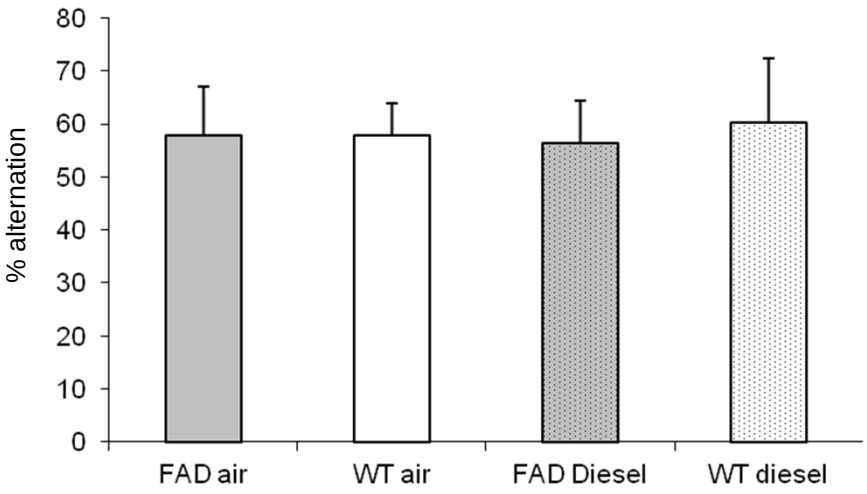
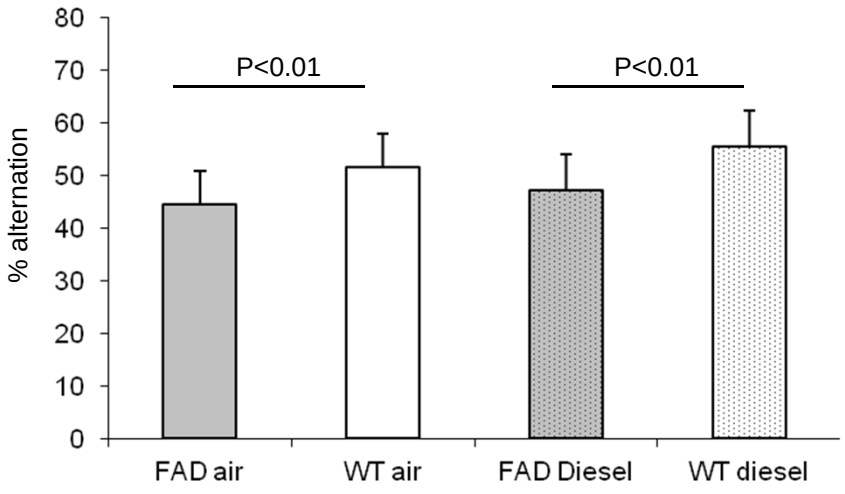
Y-maze test: Spatial working memory
(Spontaneous alternation behaviour)



3 weeks

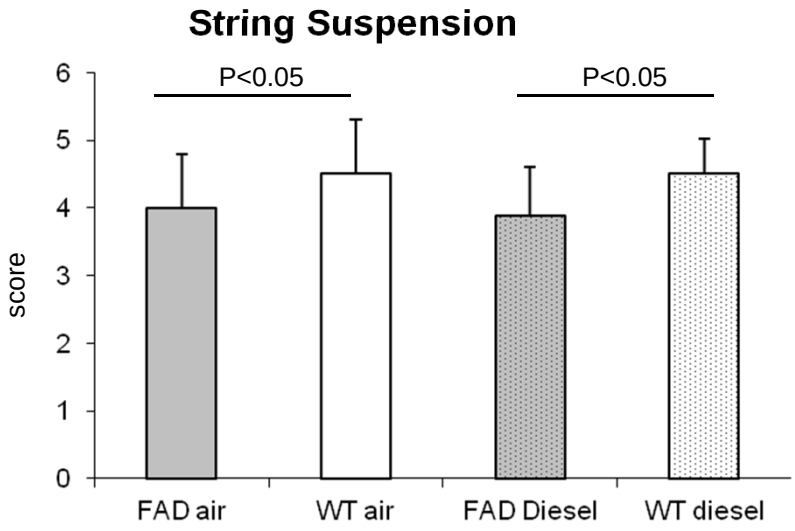


13 weeks

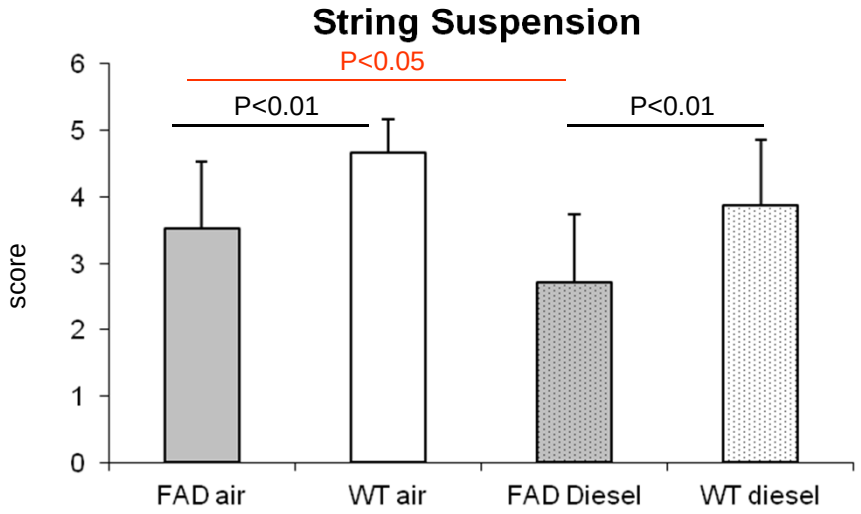


String suspension task
(Motor coordination, grip strength)

3 weeks

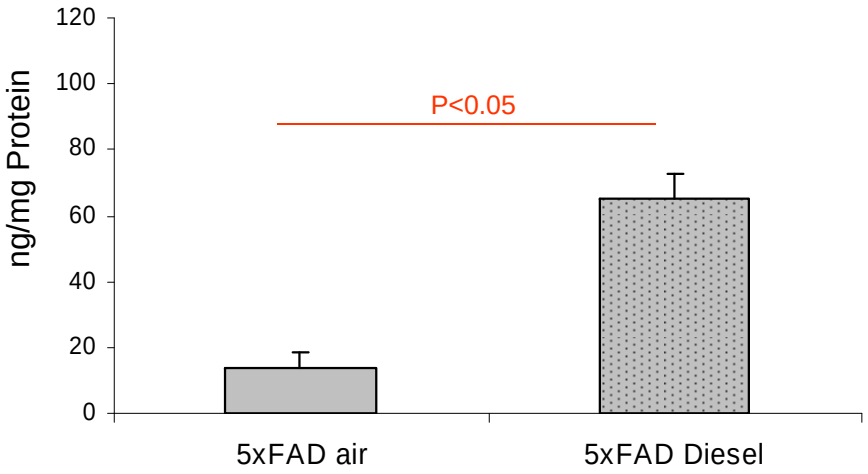


13 weeks

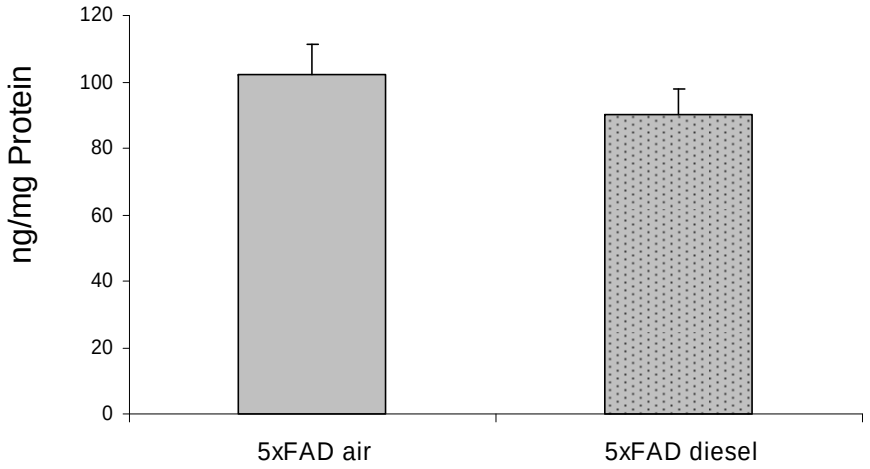


Aß42 ELISA (whole brain)

3 weeks



13 weeks



Summary

Development of “Alzheimer-like Pathology” in 5xFAD mice:

- Behaviour tests (Y-maze, X-maze, string suspension,..)
- Age dependent increase in whole brain Aß42 levels
- Formation of Aβ plaques (cortex, hippocampus)

Diesel engine exhaust exposure (3 weeks, 13 weeks):

- No significant “cognitive impairment” effects in 5xFAD mice or in wildtype mice (Y-maze, X-maze)
- “Motor function impairments” in 5xFAD mice
- Increased whole brain Aß42 levels after 3 weeks exposure
- *Quantitative evaluation of Aβ plaque formation (ongoing)*

→ DEE exposure accelerates Alzheimer phenotype in transgenic mice

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Maja Hullmann
Kirsten Gerloff
Bryan Hellack
Julia Kolling
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Anton Wessels

Irmgard Förster
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Institut für Neuropathologie, Heinrich-Heine-University Düsseldorf

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Division of Molecular Psychiatry, Georg-August-University Göttingen

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