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Identification of health effects related to environmental neurotoxic agents

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Neurodevelopmental childhood disorders

- Autism
- Dyslexia
- ADHD (attention-deficit hyperactivity disorder)
- Decreased intelligence
- Mental retardation
- Depression

Possible causal factors contributing to developmental disorders

- Roughly 28% of all major developmental disorders are attributable wholly or in part to **environmental exposures**.
- The extent to which environmental exposures contribute to the wide range of neurodevelopmental disorders is unclear.

(National Research Council, 2000).

Neurodevelopment

Prenatal Period (Months) Postnatal Period (Years)
 0 1 2 3 4 5 6 7 8 9 Birth 1 2 3 4 5 6 7 8 9 10

Cell Proliferation



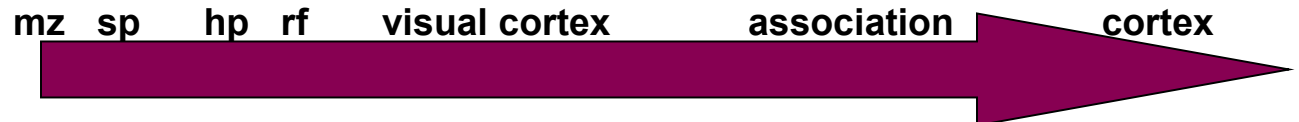
Migration of Neurons



Subplate Neurons



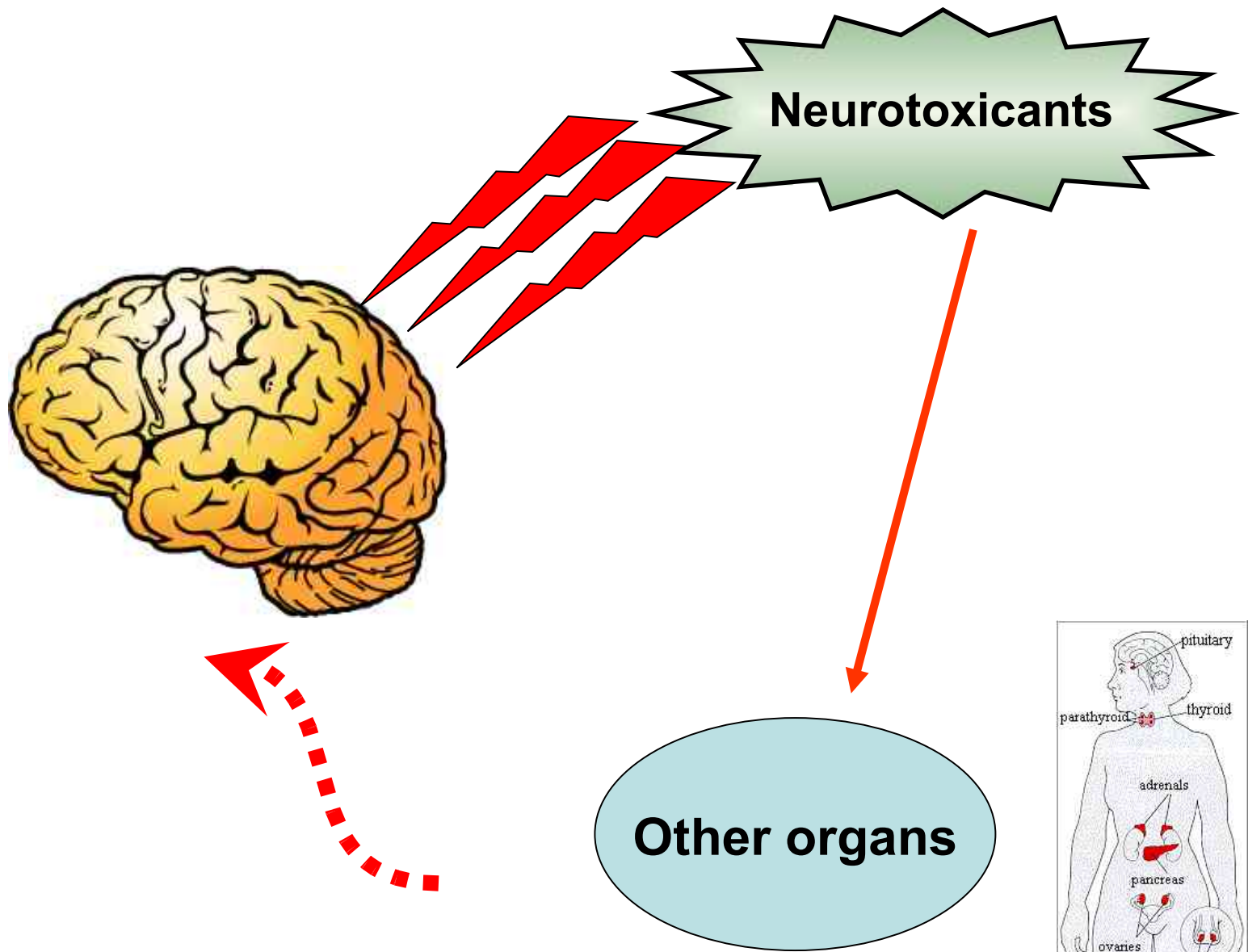
Synapse Formation



Myelination

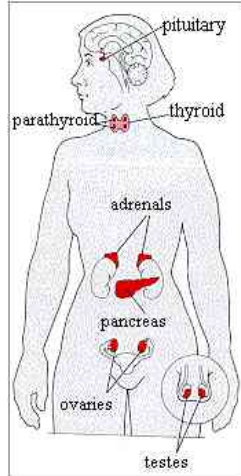


Key: mz – marginal zone; sp – subplate; hp – hippocampus; rf – reticular formation



Neurotoxicants

Other organs

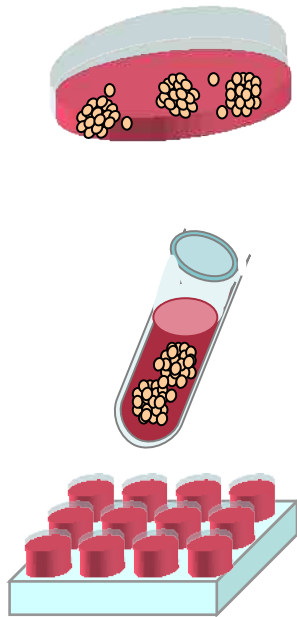


Environmental contaminants with neurotoxic potential

- 1. Dioxins and furans
- 2. Polychlorinated biphenyl (PCB)
- 3. Polybromobiphenyl (PBB)
- 4. Hexachlorobenzene (HCB)
- 5. Pentachlorophenol (PCP)
- 6. 2,4,5- Trichlorophenoxyacetic acid
- 7. 2,4- Dichlorophenoxyacetic acid
- 8. Amitrole
- 9. Atrazine
- 10. Alachlor
- 11. Simazine (CAT)
- 12. Ethyl parathion
- 13. Carbaryl
- 14. Chlordane
- 15. Oxychlordane
- 16. trans-Nonachlor
- 17. 1,2-dibromo- 3- chloropropane
- 18. DDT
- 19. DDE and DDD
- 20. Kelthane (Dicofol)
- 21. Aldrin
- 22. Endrin
- 23. Dieldrin
- 24. Endosulfan
- 25. Heptachlor
- 26. Heptachlor epoxide
- 27. Malathion
- 28. Methomyi
- 29. Methoxychlor
- 30. Mirex
- 31. Nitrofen
- 32. Toxaphene
- 33. Tributyltin
- 34. Triphenyltin
- 35. Trifluralin
- 36. Nonylphenol
- 37. Bisphenol A
- 38. Di-(2-ethylhexyl) phthalate
- 39. Butyl benzyl phthalate
- 40. Di-n-butyl phthalate
- 41. Dicyclohexyl phthalate
- 42. Diethyl phthalate
- 43. Benzo(a)pyrene
- 44. Dichlorophenol
- 45. Diethylhexyl adipate
- 46. Benzophenone
- 47. 4-Nitrotoluene
- 48. Octachlorostyrene
- 49. Aldicarb
- 50. Benomyi
- 51. Kepone (Chlordecone)
- 52. Manzeb (Mancozeb)
- 53. Maneb
- 54. Metiram
- 55. Metribuzin
- 56. Cypenethrin
- 57. Esfenvalerate
- 58. Fenvalerate
- 59. Permethrin
- 60. Vinclozolin
- 61. Zineb
- 62. Ziram
- 63. Dipentyl phthalate
- 64. Dihexyl phthalate
- 65. Dipropyl phthalate
- 66. Styrens
- 67. n-Butylbenzene
- 68. Cadmium
- 69. Lead
- 70. Mercury

Our approach to investigate mechanisms of developmental neurotoxicity

In vitro  ***In vivo***



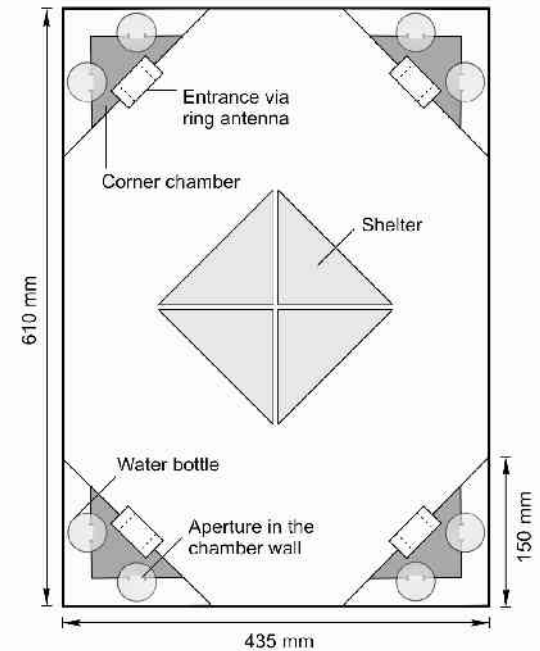
Morphological,
cytochemical,
biochemical and
molecular analyses



(modified from McEwen and Schmeck, 1994)

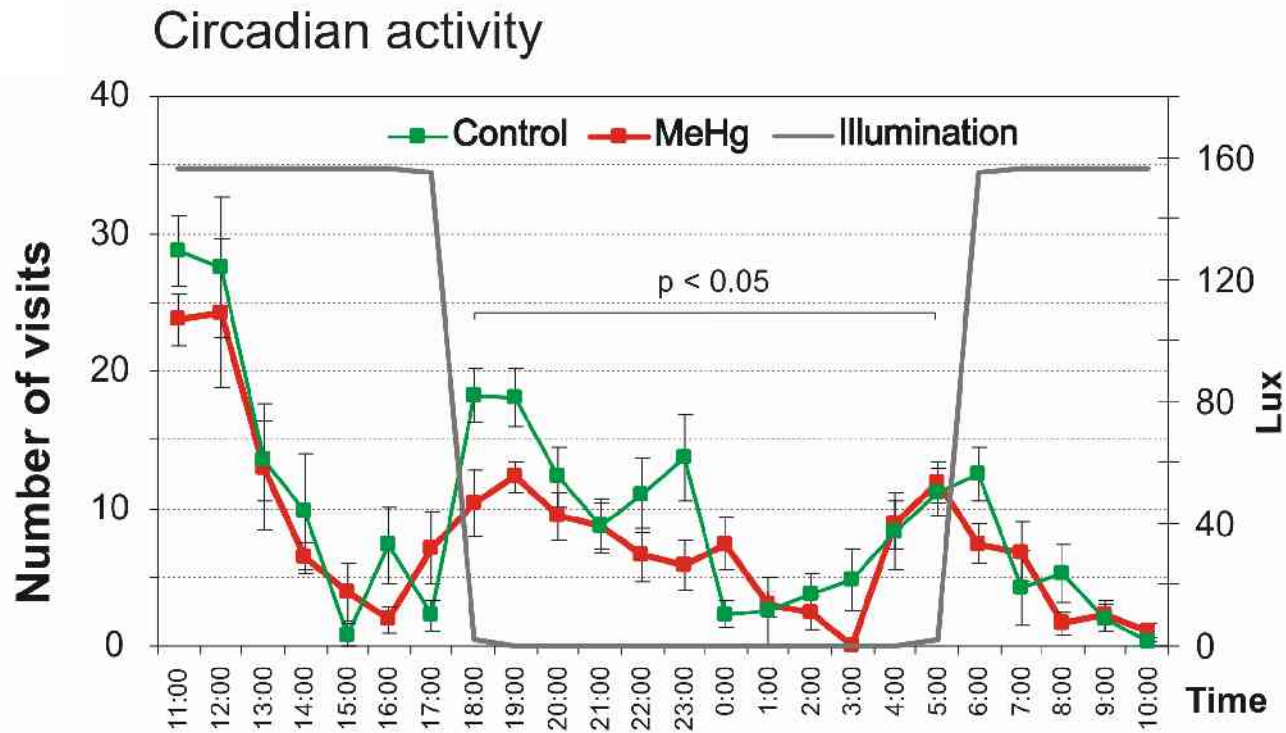
Behavioral,
histochemical and
molecular analyses

IntelliCage[®]

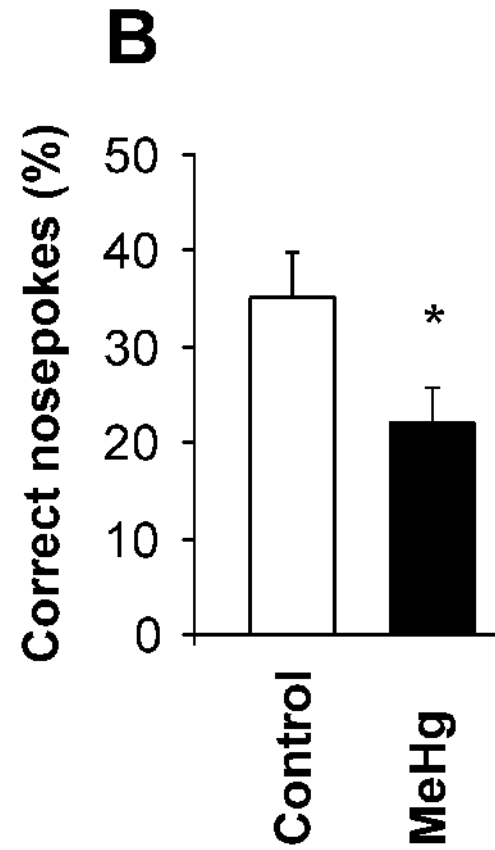
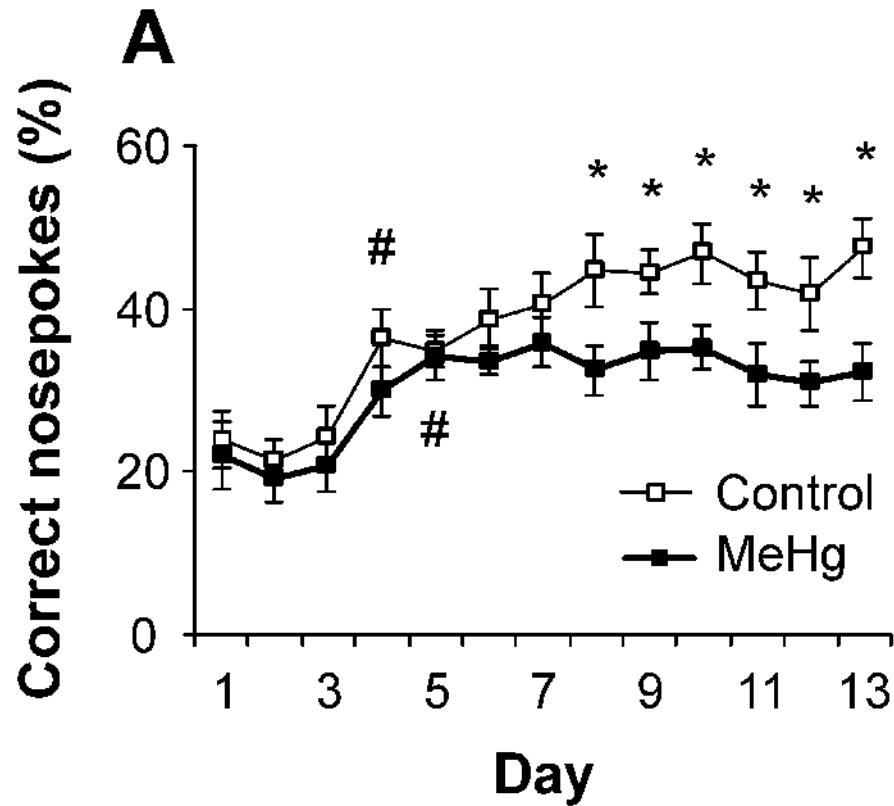


- Spontaneous behavior: exploration, novelty reaction, circadian activity
- Spatial preference and avoidance
- Operant learning
- Visual discrimination
- Taste preference

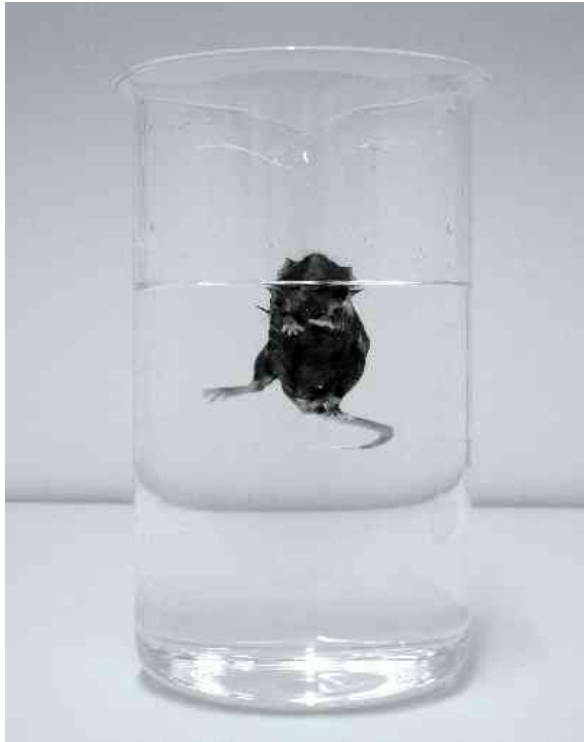
Decreased exploratory activity in MeHg-exposed male mice



Developmental exposure to MeHg impaires learning and memory in male mice

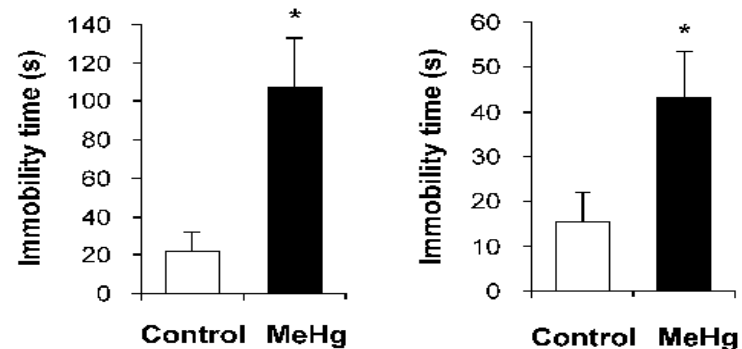


Depression-like behavior in MeHg-exposed male mice

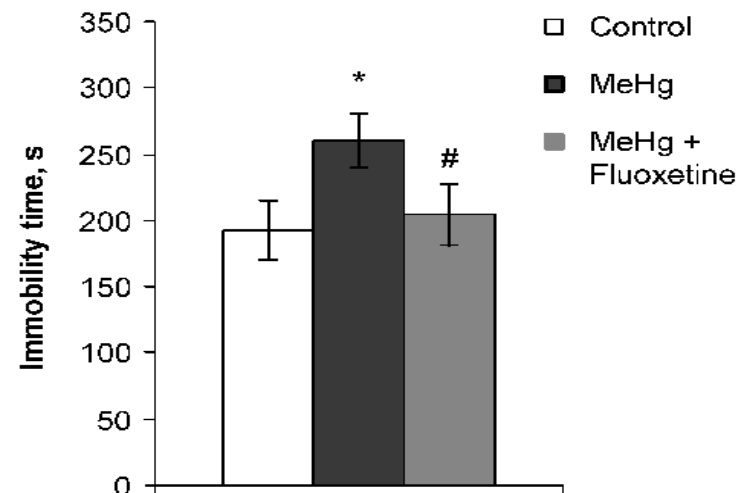


In the FST rodents alternate active responses and immobility after placement in a beaker of water. In this paradigm, the more time an animal spends in an inactive or immobile state versus active state is interpreted as a measure of depressive-like behavior (Porsolt et al. 1977)

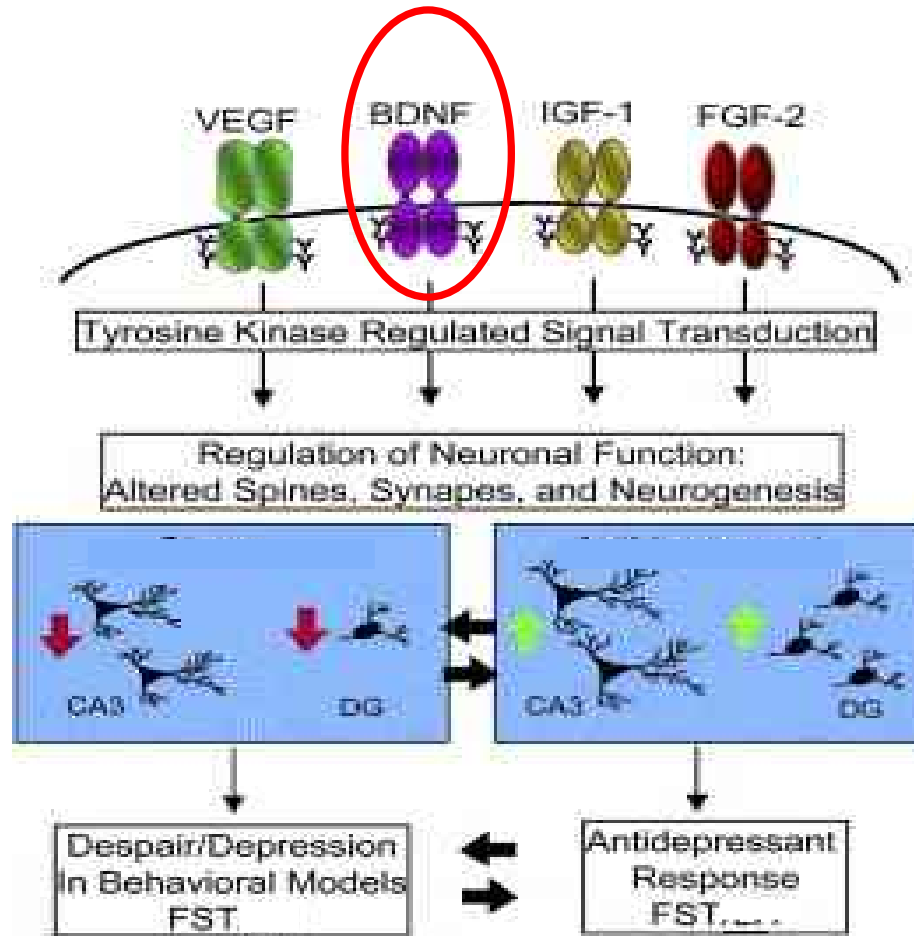
Depression-like behavior in the FST



Effect of antidepressants (fluoxetine 10 mg/kg, 21 days)

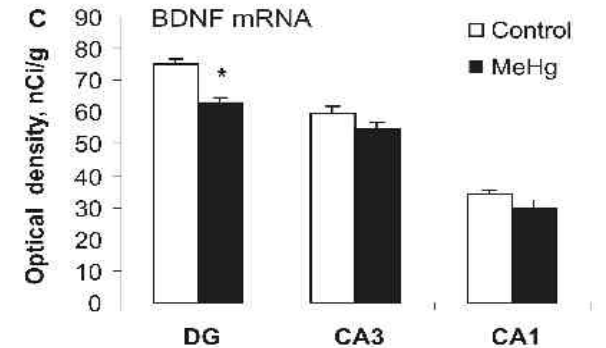
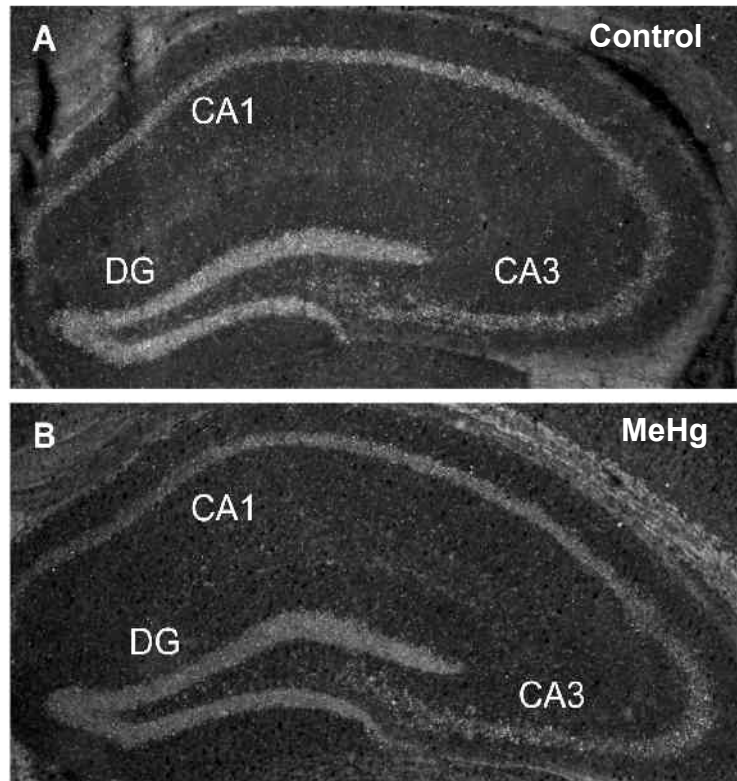


Role of growth factors in depression

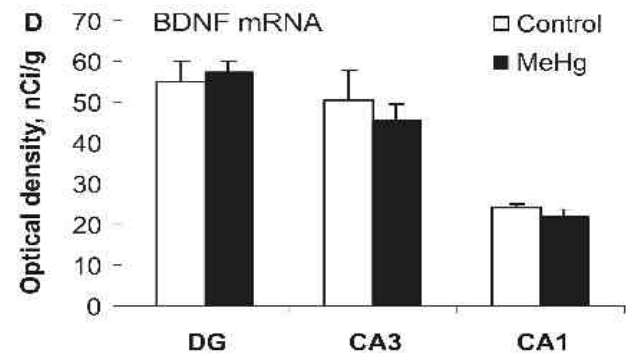


(Modified from Duman & Monteggia, 2006).

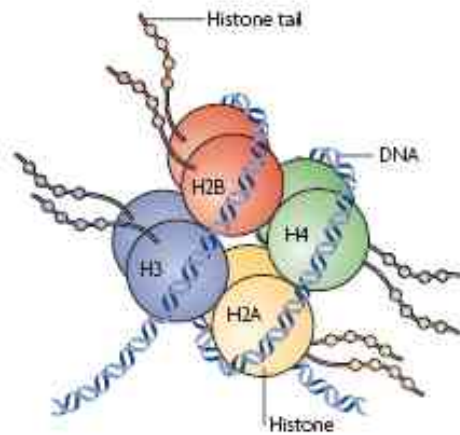
Decreased BDNF mRNA levels in the hippocampus of MeHg-exposed male mice



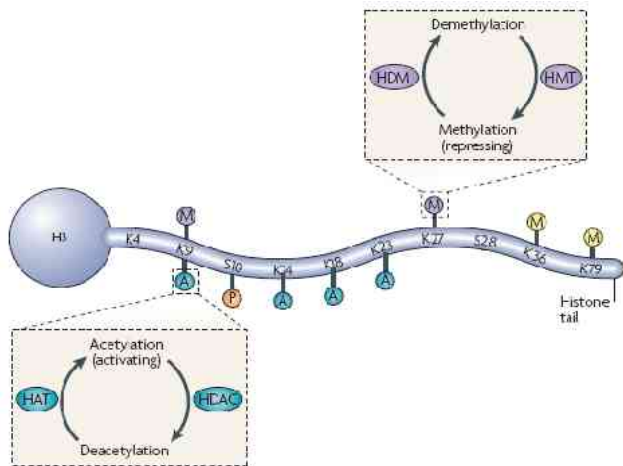
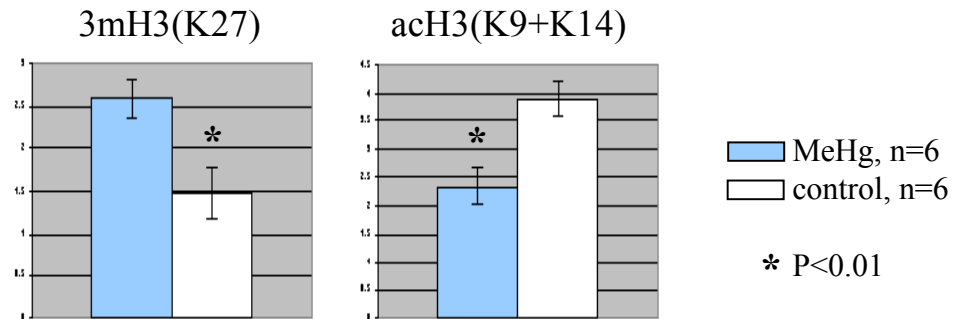
Antidepressant response



Epigenetic changes of BDNF gene induced by MeHg

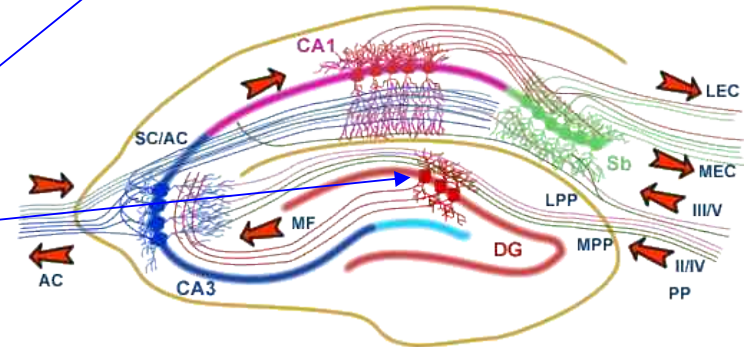
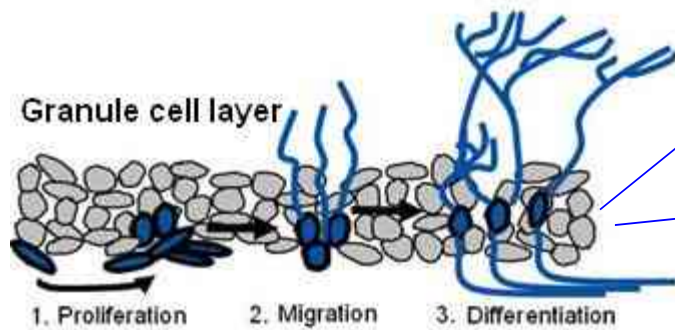
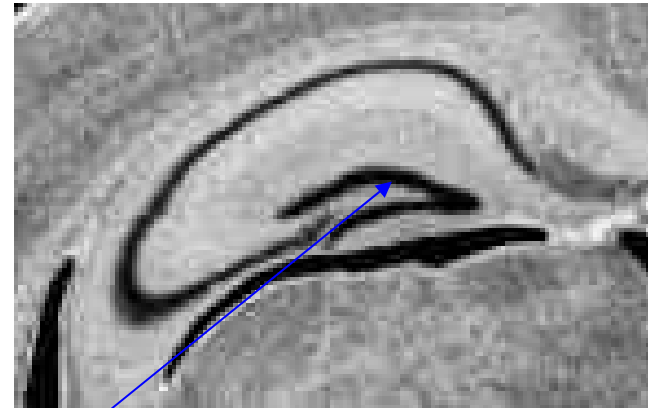
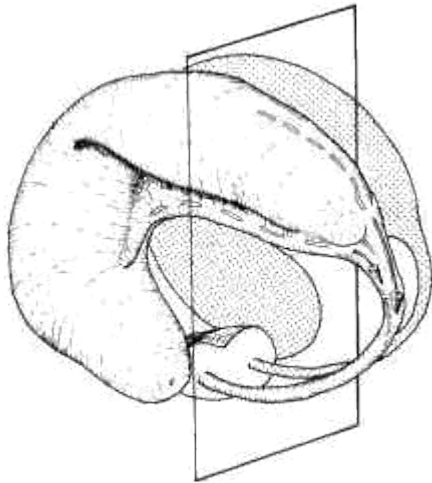


Chromatin immunoprecipitation assay

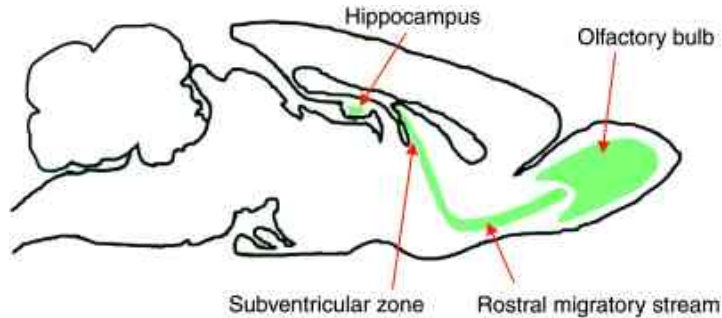


H3 histone hypermethylation and hypoacetylation as well as DNA hypermethylation at the *Bdnf* gene promoter IV have been found in hippocampus of 14-month-old MeHg-exposed mice

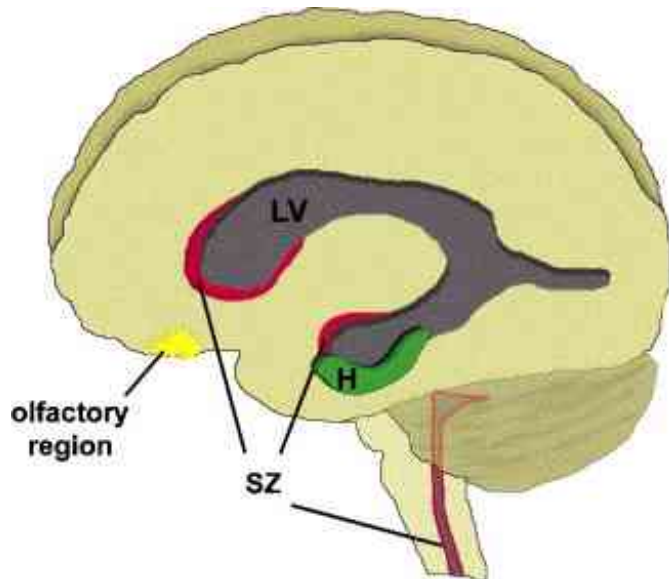
Functions of Brain-Derived Neurotrophic Factor (BDNF): migration, differentiation and long-term survival of the newborn neurons



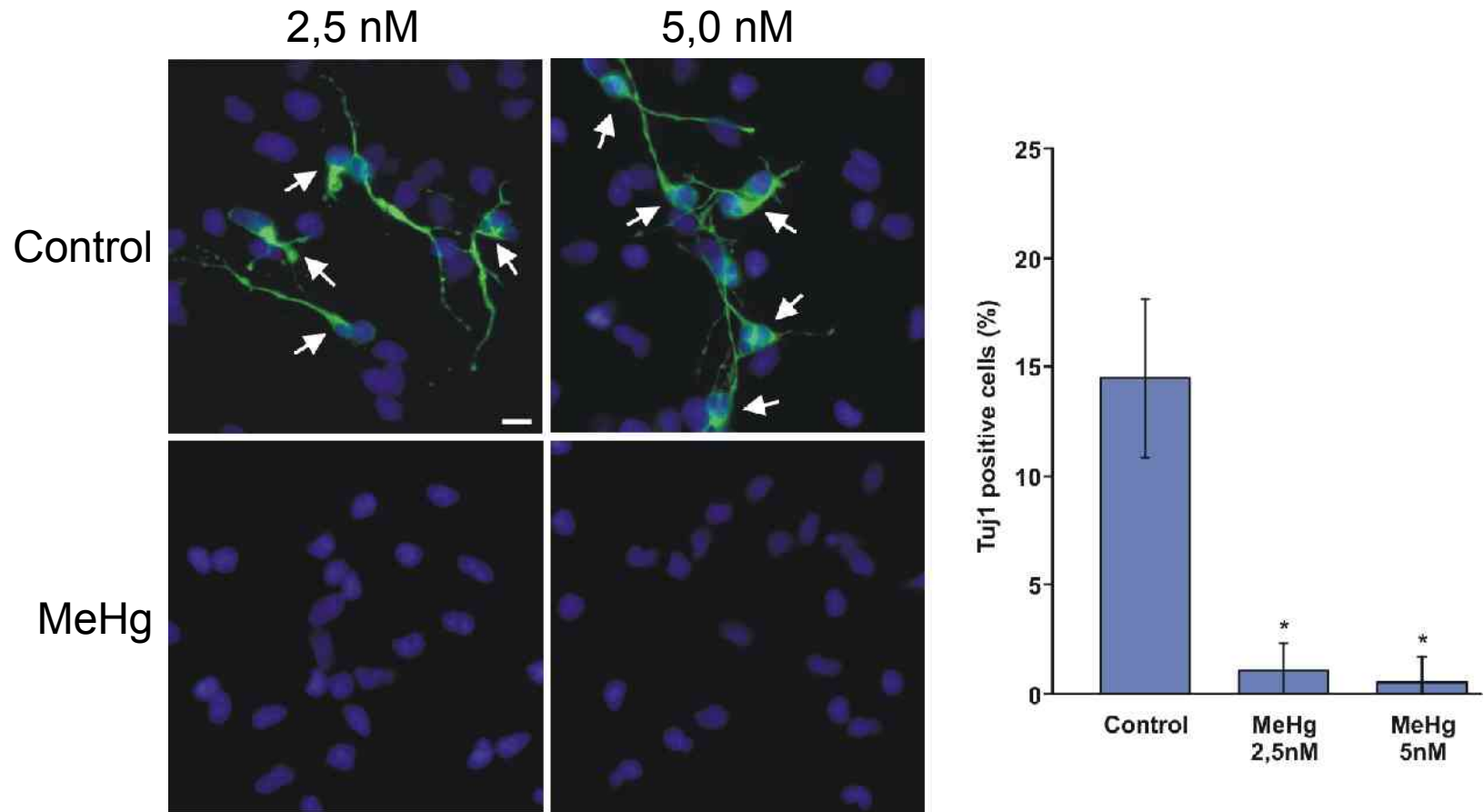
Adult Neural Stem Cells (NSC)

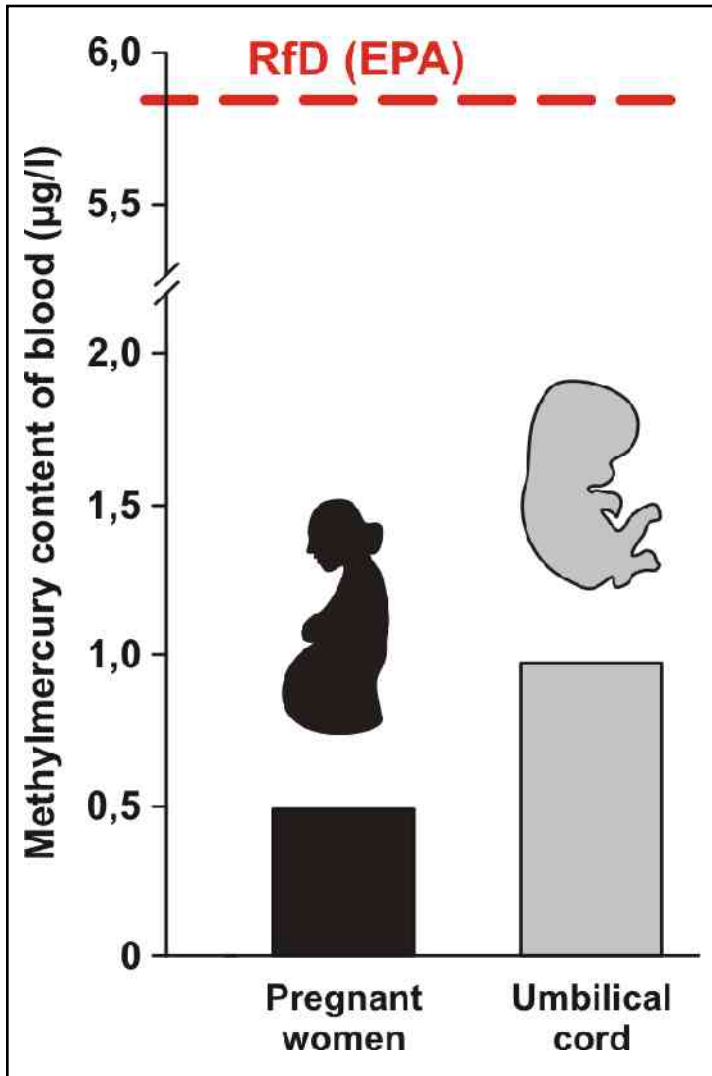


- **The capability for self-renewal is important for brain normal functions, including learning, memory, and emotional responses.**



MeHg decreases spontaneous neuronal differentiation of NSC





MeHg Reference Dose for human exposure.

Concentrations comparable to the ones used in our experiments.

Conclusions

The combined use of *in vivo* and *in vitro* experimental models is a valid strategy to identify potential neurotoxic agents.

Epigenetic changes are critical players in the onset of neurotoxicity.

Studies on the interaction between environmental and genetic factors are needed to move forwards the field of neurotoxicology.



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The Neurotoxicology Group

*Neuroscience Center
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Eero Castrén
Nina Karpova



**Toxic threats
to the
developing
nervous system**



European Commission

The Swedish Research Council FORMAS