Plant neurotoxins and brain development

Implications for encephalization in *Homo*

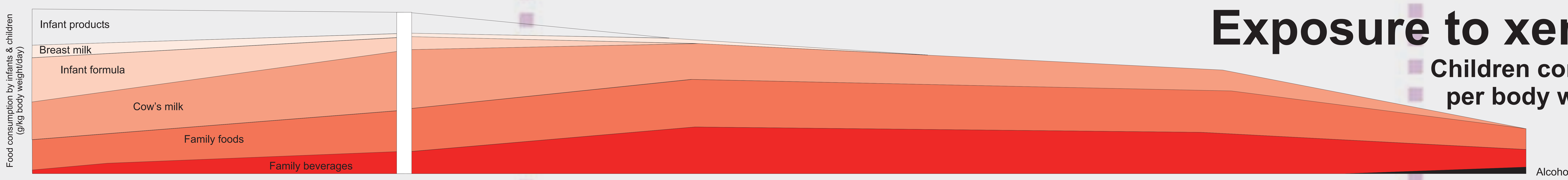
"Flying solo"

Foods selected and detoxified by immature organism

Exposure to xenobiotics

Children consume more food per body weight than adults

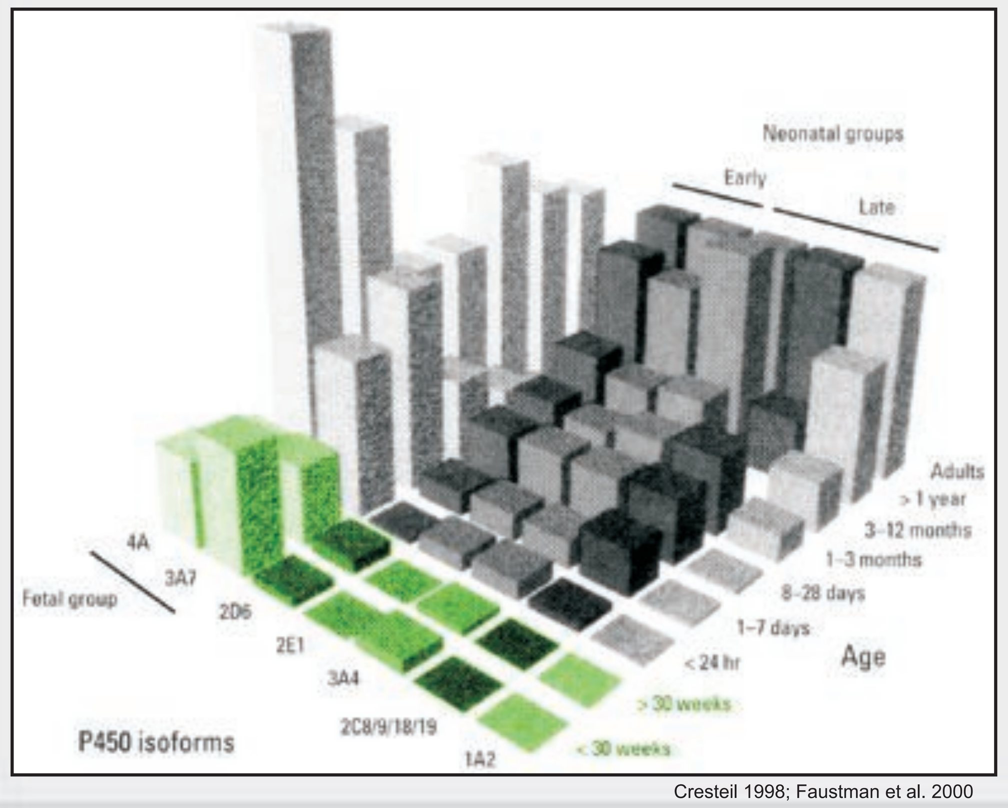
Mother's bloodstream and milk



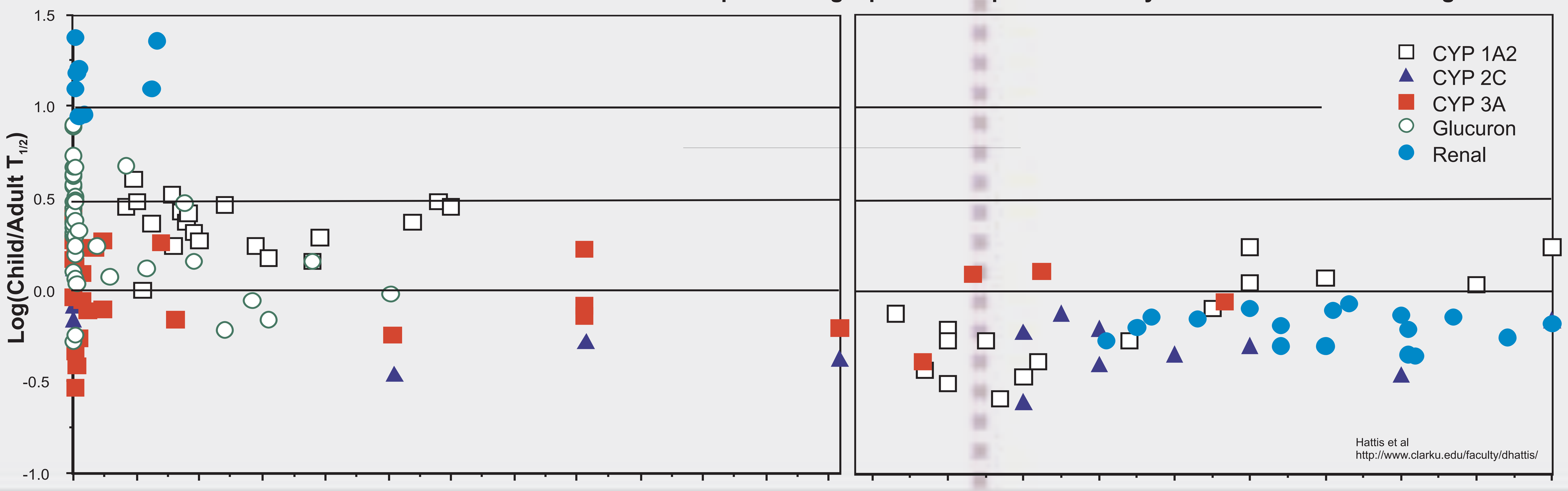
Diet composition: infants and children

Development of xenobiotic metabolism

Xenobiotic metabolizing enzymes



Xenobiotic metabolism: Pharmacokinetics for 40 therapeutic drugs–proxies for plant toxins–by mode of elimination and age



Vulnerabilities of children relative to adults

Larger brain/body-weight ratio
Greater blood flow through the CNS
More permeable blood-brain barrier
Immature enzyme function in first year

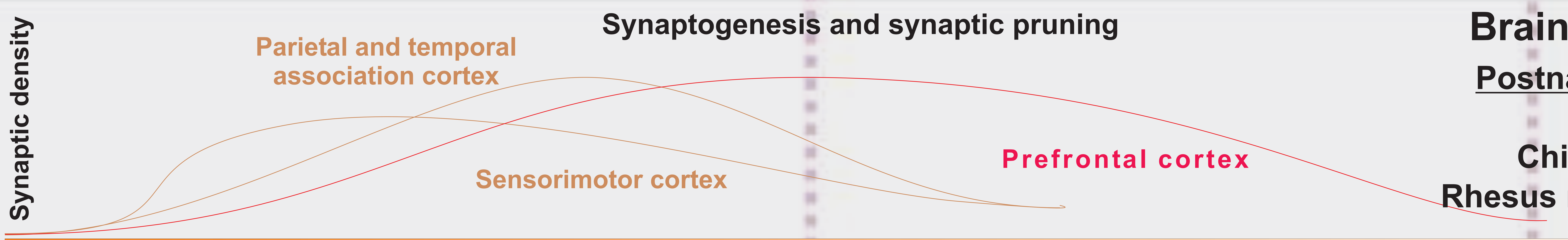
Advantages of children relative to adults

Larger liver/body-weight ratio and faster xenobiotic clearance after the age of one

Brain development

Neurulation

Cell proliferation and migration



Myelination

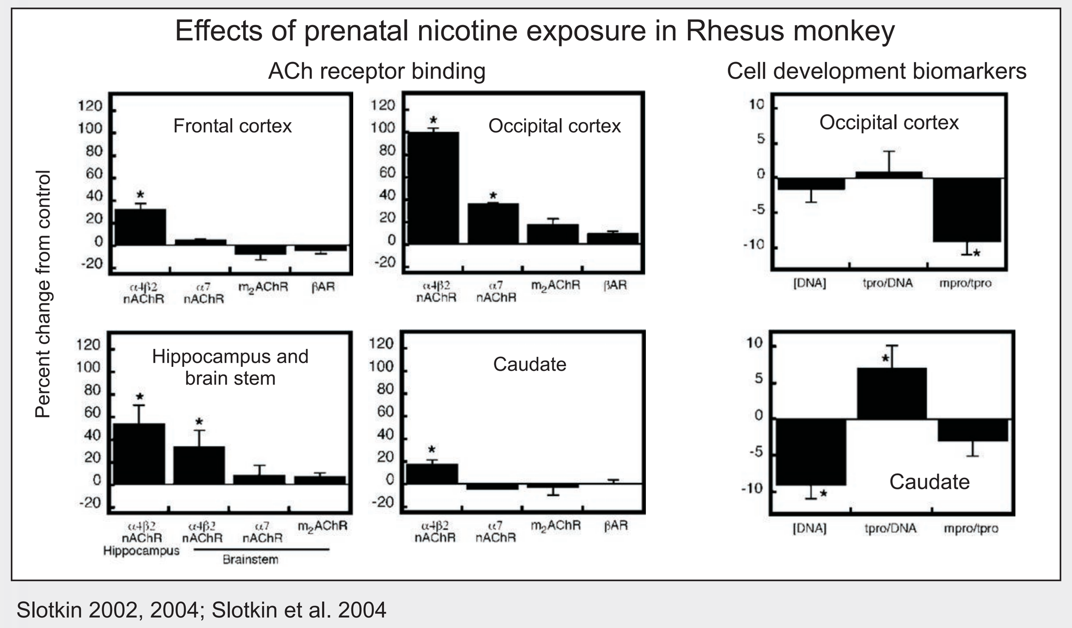
Postnatal brain growth

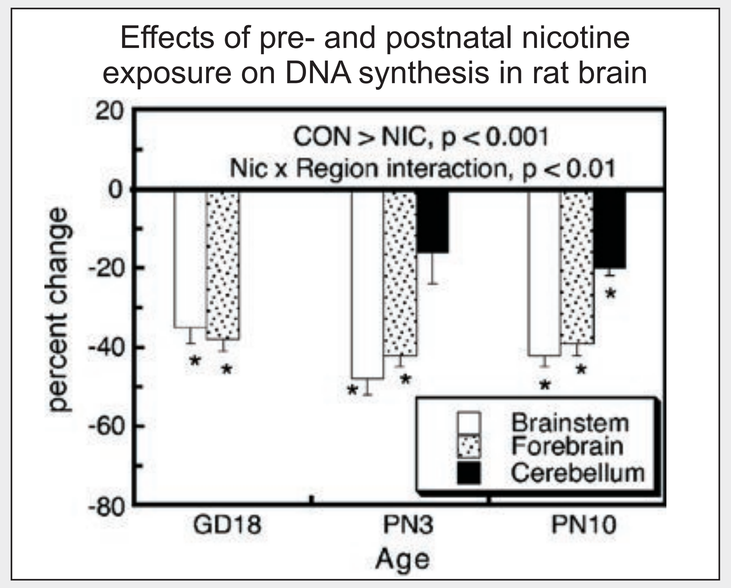
Humans	75%
Chimpanzees	50%
Rhesus macaques	25%

Experience-dependent synapse formation and dendritic arborization

Thompson & Nelson 2001; Casey et al. 2005

Effects of plant neurotoxin nicotine on developing nervous system





Successful development of the mammalian brain depends crucially on highly coordinated inter- and intracellular signaling cascades. Expression of several nicotinic acetylcholine receptors (nAChRs) subunit mRNAs, for example, is increased in fetal vs. adult brains, suggesting an important developmental role for nAChRs in modulating dendritic outgrowth, establishment of neuronal connections and synaptogenesis. Serotonergic receptor levels peak in fetal or early neonatal life, later declining to adult levels. And in the dopamine system, the highest number of D1 and D2 receptors occurs in the immature brain. Developmental diseases characterized by severe cognitive deficits, such as Down syndrome and autism, have been linked to disruption of serotonergic and other neurotransmitter systems.

Plants evolved to protect themselves by producing toxins targeting and disrupting key cell signaling pathways in the peripheral and central nervous system of herbivores. Nicotine targets nAChRs, ergot alkaloids target serotonin receptors, and cocaine targets the dopamine system, for example. Exposure to such plant neurotoxins during evolution plausibly constrains encephalization for several reasons:

- More neurons, glia, and synapses more targets for plant neurotoxins.
- Longer development time greater probability of disruption by plant neurotoxins.
- More postnatal development greater exposure to plant neurotoxins.
- More "flying solo", i.e., brain development fueled by foods selected and detoxified by immature organism greater exposure to plant neurotoxins.

The high quality diet (e.g., meat) and detoxification technologies (e.g., cooking) of *Homo* probably reduced its exposure to plant neurotoxins relative to other primates, as suggested by a reduced compliment of xenobiotic metabolizing enzymes, lower enzyme activity, and other evidence. This could have been an important factor in the encephalization of our genus.

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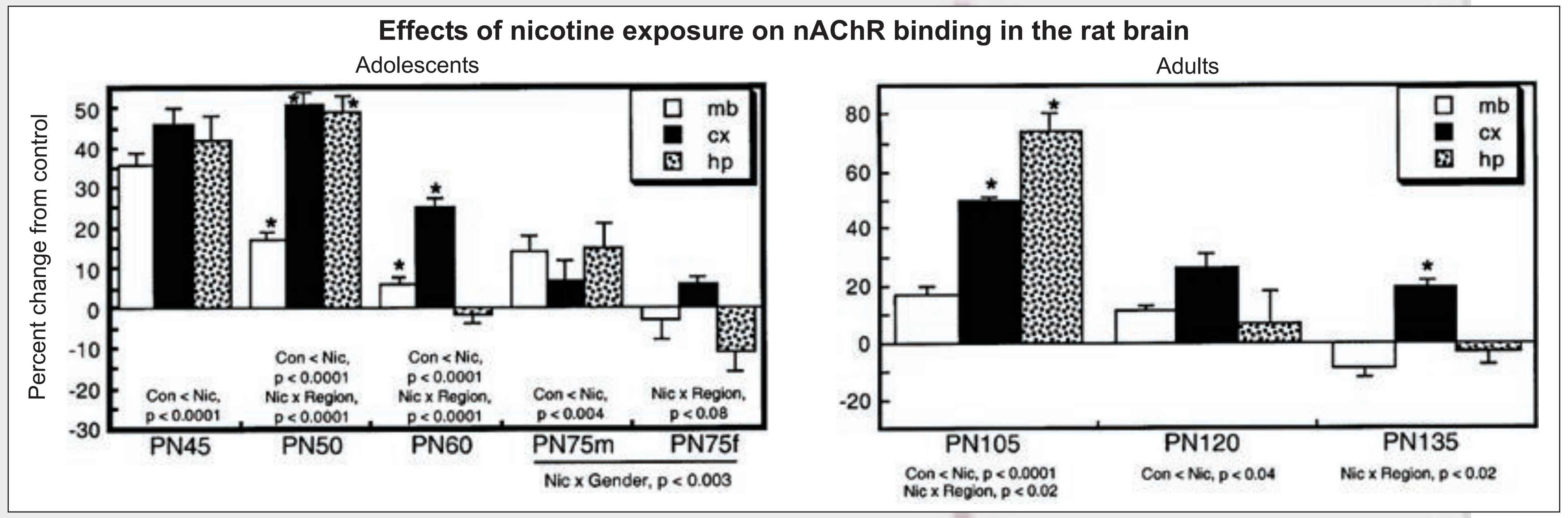

-8 -6 -4 -2 Birth 2 4 6 8 10 12
Months

2 4 6 8 10 12 14 16 18 20
Years