

Global Environmental Health

February 15, 2007

How May Environmental Factors Impact Potential Mechanisms in Humans?

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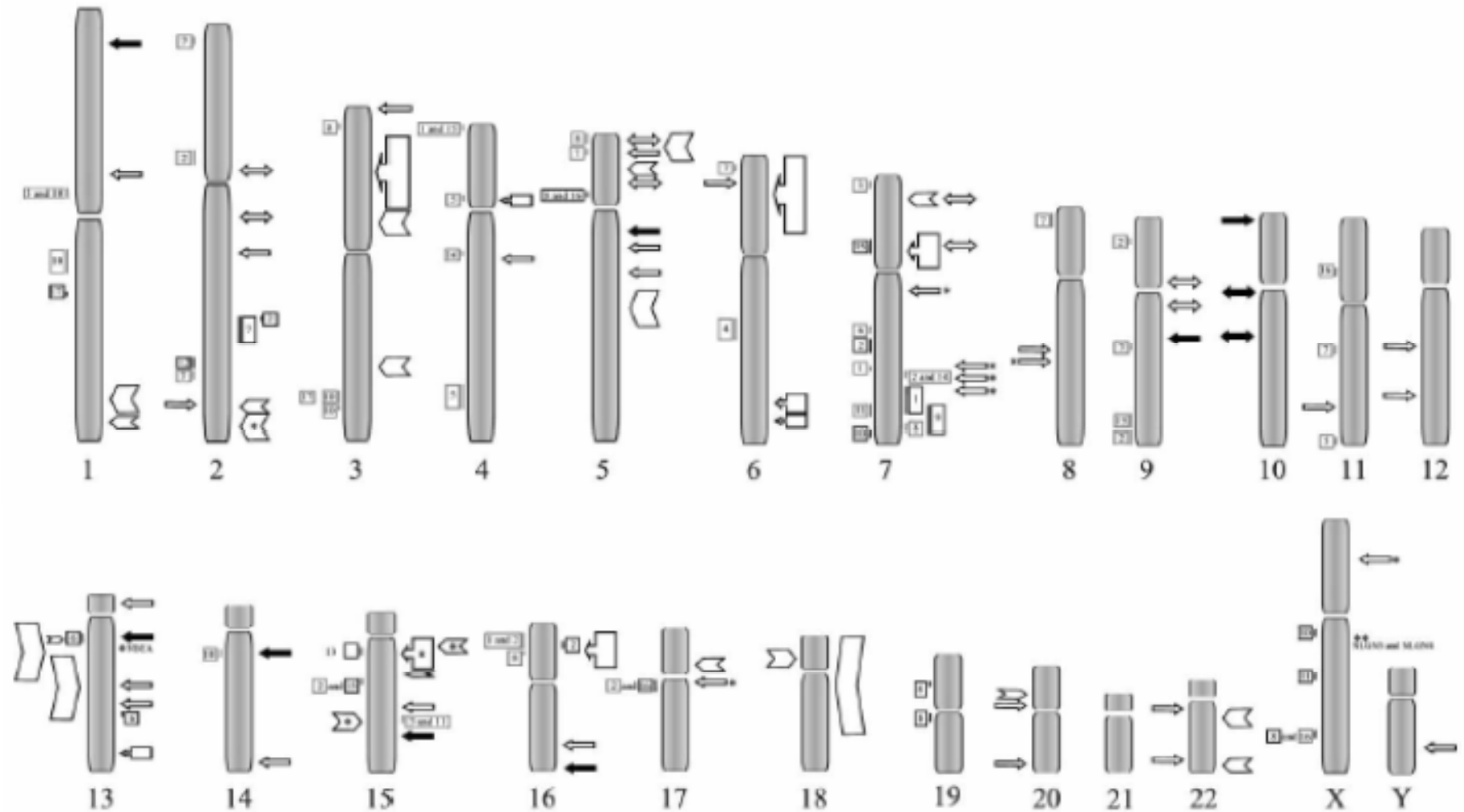
Center for Children's Environmental Health
The M.I.N.D. Institute
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Autism is a Complex Disorder

Multiple genes are involved in conferring autism susceptibility



Scope of the Problem

- ~4,000,000 births per year in U.S.
- ~ 120,000 major defects reported for live-born infants
 - structural defects (neural tube, heart)
 - growth retardation
 - functional deficits
- Underestimate: most neurological and behavioral problems are not diagnosed until early childhood or young adulthood
- At present, the causes of the majority of developmental defects are not understood.
- ~ 3% of all developmental defects are attributable to exposure to toxic chemicals
 - ~ 25% of all developmental defects may be due to a combination of genetic and environmental factors.

What we don't know about environmental triggers ----quite a bit!

>53,000 commercially important chemicals

- *NTP* survey of 49,000 industrial chemicals
~80% lack adequate toxicity data (especially DNT)
- 3,400 pesticides are more heavily regulated
~64% lack adequate data for risk assessment
- 3,400 cosmetic ingredients
~74% lack adequate data for risk assessment
- 8,600 food additives
~80 % lack adequate data for risk assessment

Toxcast™ Program

Prioritizing Toxicity Testing of Environmental Chemicals

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

Little is known about:

Additivity

Synergism

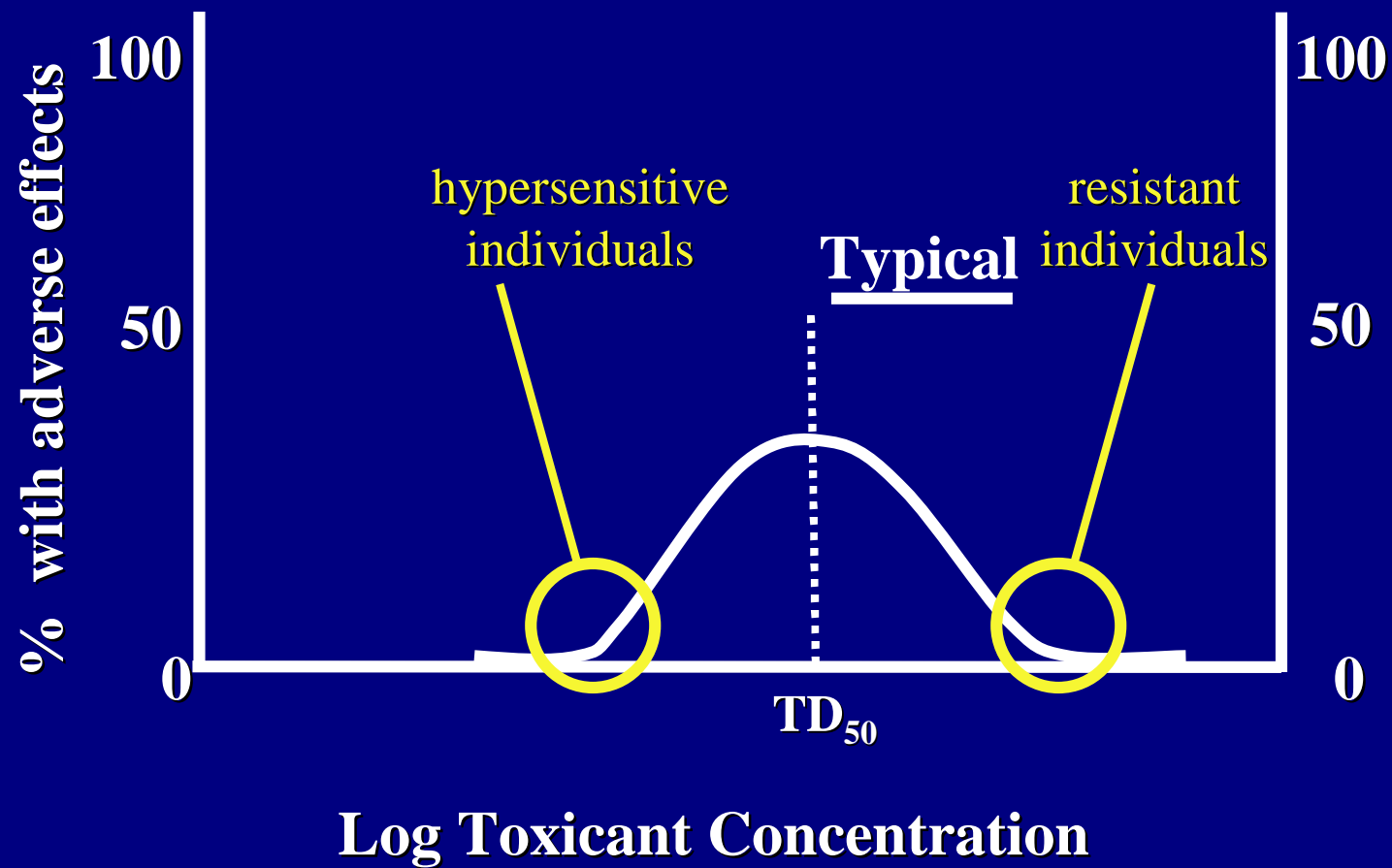
Antagonism

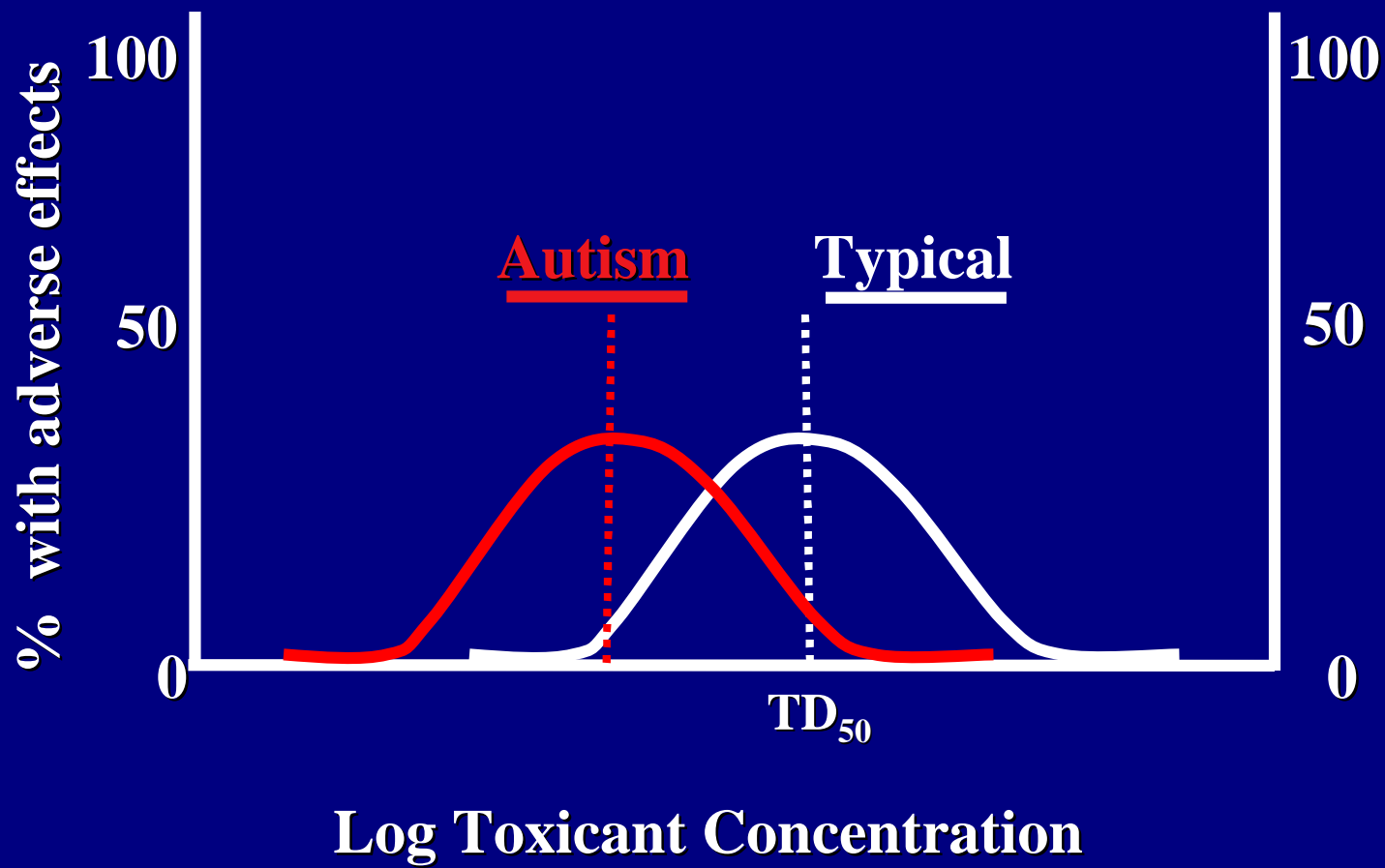
Relative timing

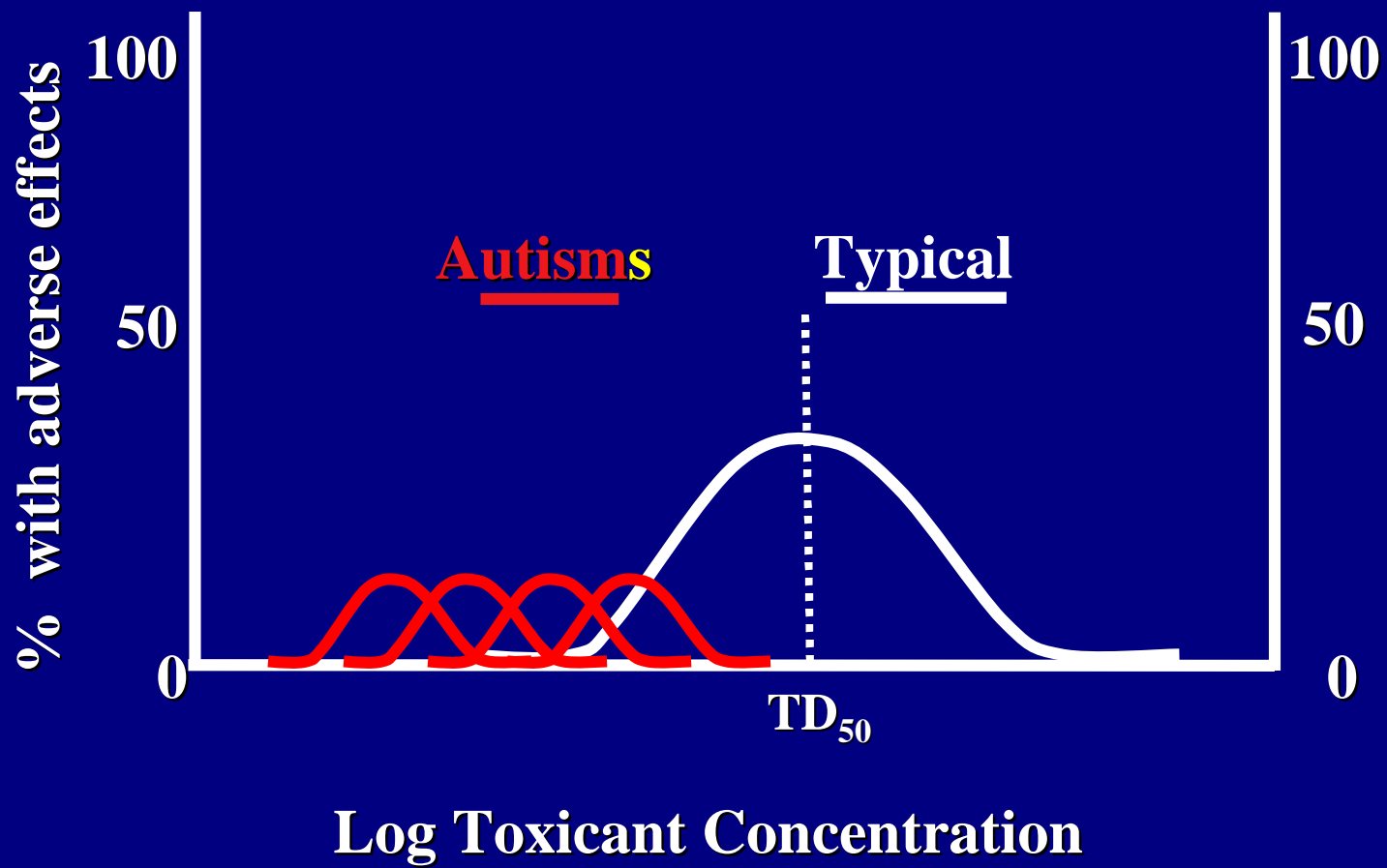
Autism is a Complex Disorder

Autism is a multi-system disorder whose outcome is likely to be more profoundly impacted by environment than other disorders and diseases.

What are the possible mechanisms involved?







Framework for understanding gene-environment interactions impacting autism risk

Hypothesis generating concept:

Genetic susceptibilities \times environmental exposures \times *timing* = prevalence and severity of developmental disorders

Mutations within Ca²⁺ channels are associated with autism susceptibility

Timothy Syndrome

Cell, Vol 119, 19-31, 1 October 2004

Ca_v1.2 Calcium Channel Dysfunction Causes a Multisystem Disorder Including Arrhythmia and Autism

Igor Splawski,¹ Katherine W. Timothy,² Leah M. Sharpe, Niels Decher,³ Pradeep Kumar,³ Raffaella Bloise,⁴ Carlo Napolitano,⁴ Peter J. Schwartz,^{5,6} Robert M. Jose, Karen Condouris,⁷ Helen Tager-Flusberg,⁷ Silvia G. Priori,^{4,5} Michael C Sanguinetti,³ and Mark T. Keating¹

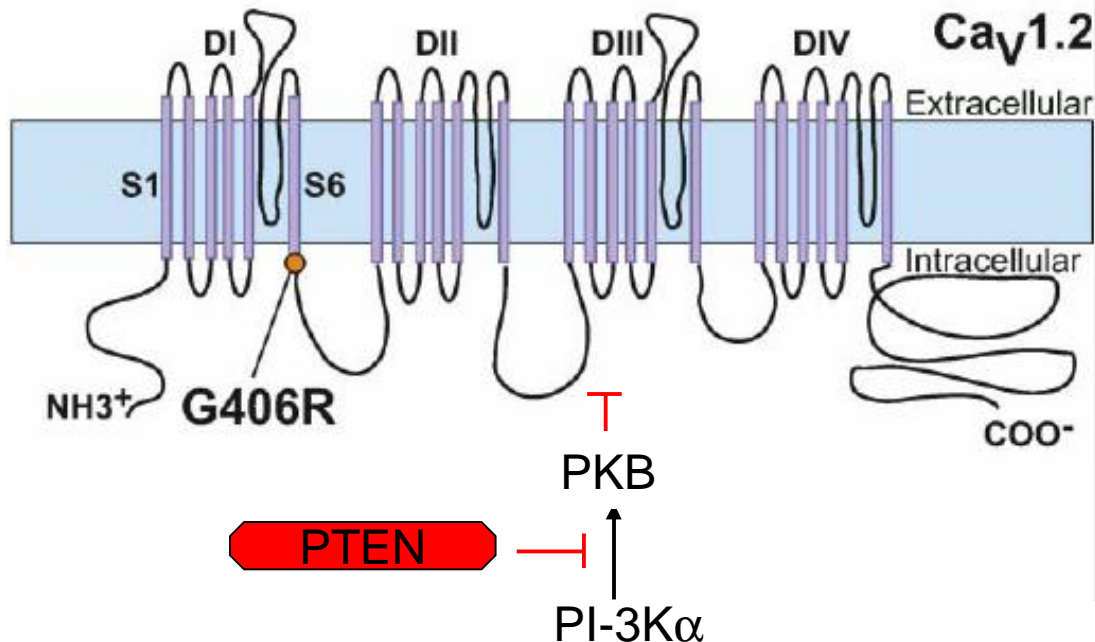


Table 1. Phenotypic Features of Timothy Syndrome

Phenotype	Affected ^a (%)
Heart	
QT prolongation	100
Arrhythmia	
(1) Ventricular tachyarrhythmia	71
(2) Bradycardia, AV block ^b	94
Patent ductus arteriosus	59
Patent foramen ovale	29
Ventricular septal defects	18
Tetralogy of Fallot	6
Cardiomegaly	35
CNS	
Autism	60
Autism spectrum disorders	80
Mental retardation	25
Seizures	21
Umbilical cord	
Two vessel	13
Gastrointestinal	
Gag reflex	31
Skin	
Syndactyly	100
Bald at birth	100
Face	
Dysmorphia	53
Abnormal immune responses	50%

Defective/deficient GABA_A Receptors in Autisms

- **Epigenetic mechanisms**

MeCP2-deficiency associated with down regulation of GABRb3

(Samaco *et al* 2005, *Hum Mol Genet* **14**(4), 483-92)

- **Complex gene-gene interactions**

Polymorphisms at GABRa4 are involved in the etiology of autism, interaction with GABRb1 increases autism risk

(Ma *et al*, 2005, *Am J Hum Gen* **77**, 377)

- **Polymorphisms**

GABRg1, GABRb3 genes...

(Vincent *et al*, 2006 *J Med Gen* **43**, 429; Ashley-Koch *et al*, 2006 *Ann Hum Gen* **70**, 281)

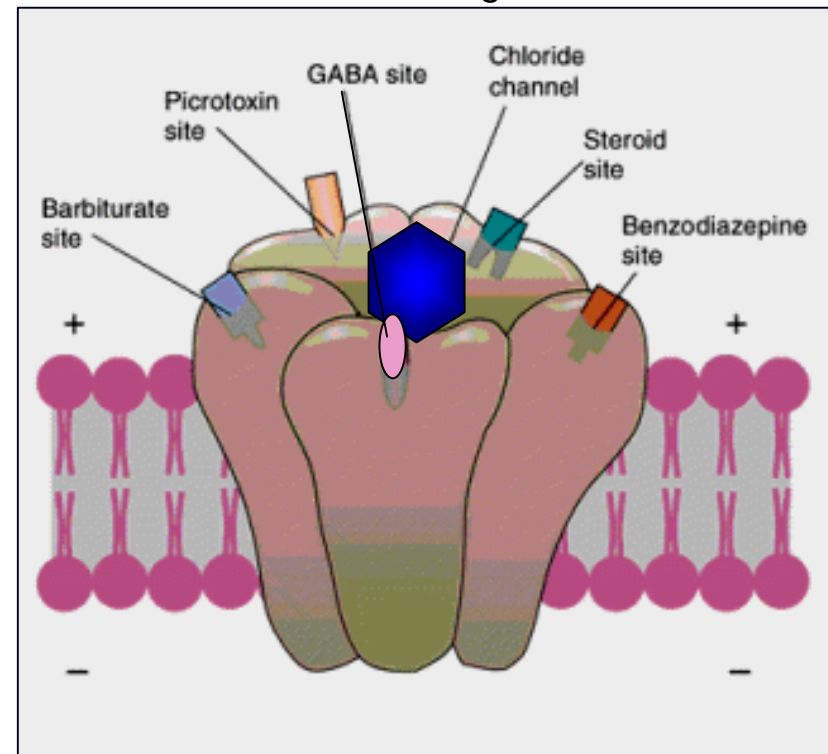
**Pesticides (Chlorinated hydrocarbons block GABA_A receptors)
PCBs alter the balance of excitation and inhibition in the
developing brain**

Pesticides that block the pore GABA_A receptors

Chlorinated hydrocarbon pore blockers

Lindane (head lice, scabies)
Hepatchlor (1988)
Chlordane (1988)
Diledrin (1987)
Kepone (1978)
Toxaphene (1990)

Schematic illustration of a GABA_A receptor with its binding sites



To appreciate the effectiveness of these materials as termiticides, consider that wood and wooden structures treated with chlordane, aldrin, and dieldrin in the year of their development are still protected from damage--more than 55 years!

Pesticides that antagonize GABA_A Receptors

Non-Competitive GABA antagonist

Fipronil (4-alkyl-1-phenylpyrazole)

>800 tons applied in 2000

Regent®

Goliath®

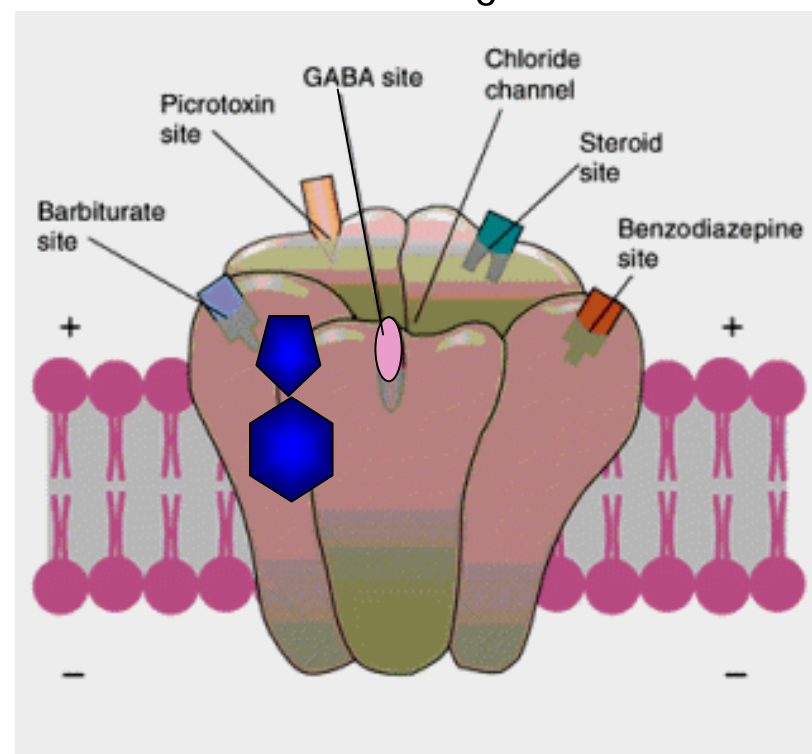
Nexa®

Adonis®

Chipco Choice®

Frontline®

Schematic illustration of a GABA_A receptor with its binding sites



“Structure-activity studies described here reveal that fipronil retains its very **high binding potency at the human beta3** and house fly gamma-aminobutyric acid (GABA) receptors”

GABA receptor antagonists and insecticides: common structural features of 4-alkyl-1-phenylpyrazoles and 4-alkyl-1-phenyltrioxabicyclooctanes

Sammelson RE, Caboni P, Durkin KA, Casida JE

Bioorg Med Chem. 2004 **12(12)**:3345-55.

Gene-Environment interactions altering the balance of excitatory and inhibitory circuits

Genes, Brain and Behavior (2003) 2: 255–267

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Model of autism: increased ratio of excitation/inhibition in key neural systems

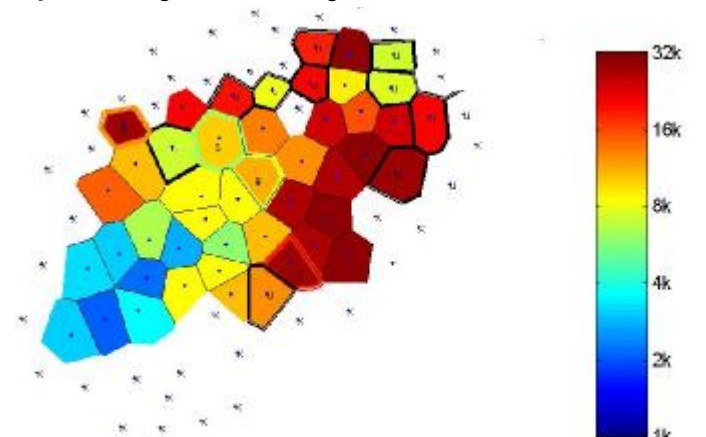
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Normal receptive field within primary auditory cortex (PN35-50)



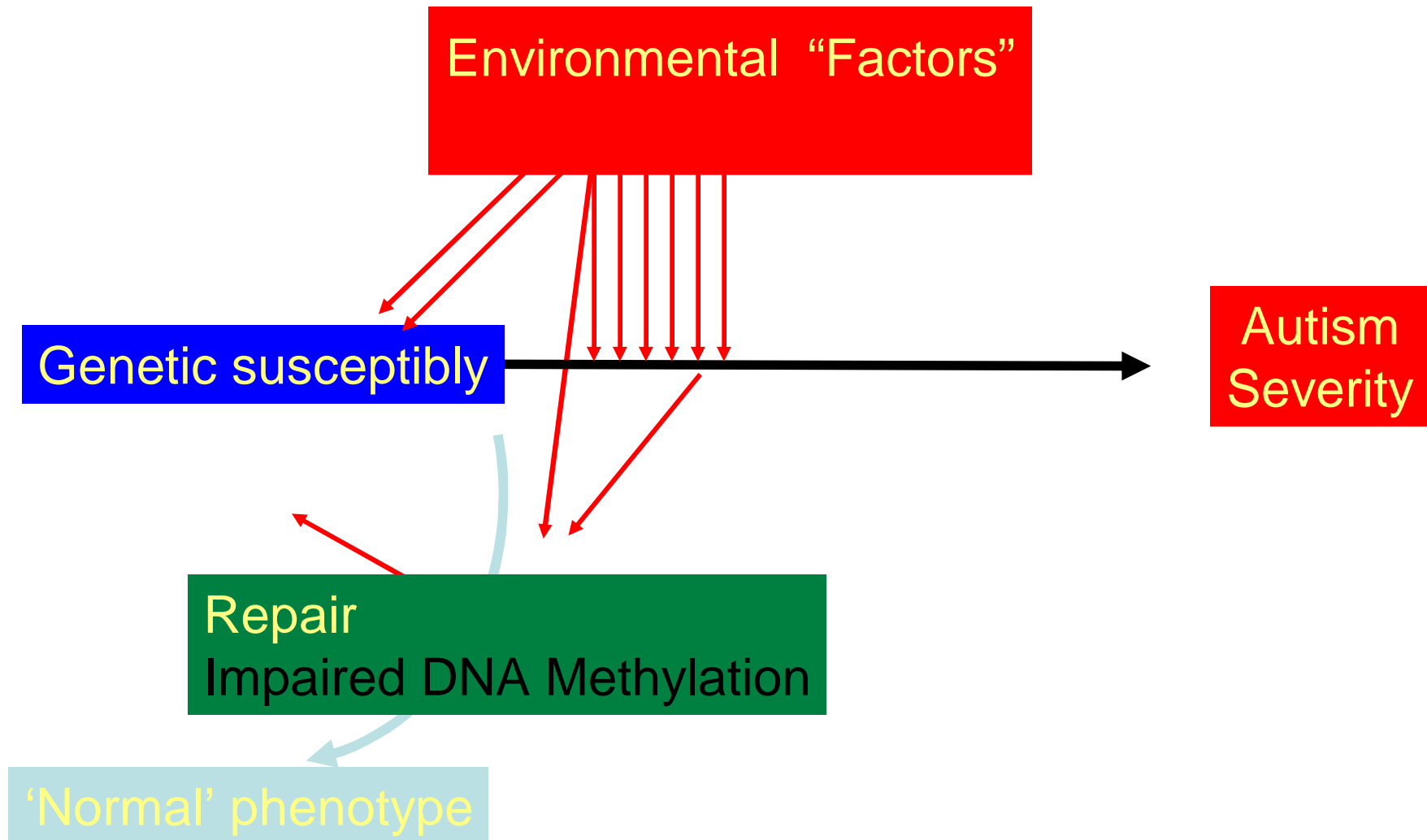
Perinatal 2,2,3,5,6-pentachlorobiphenyl



Kenet et al (2007) PNAS in press

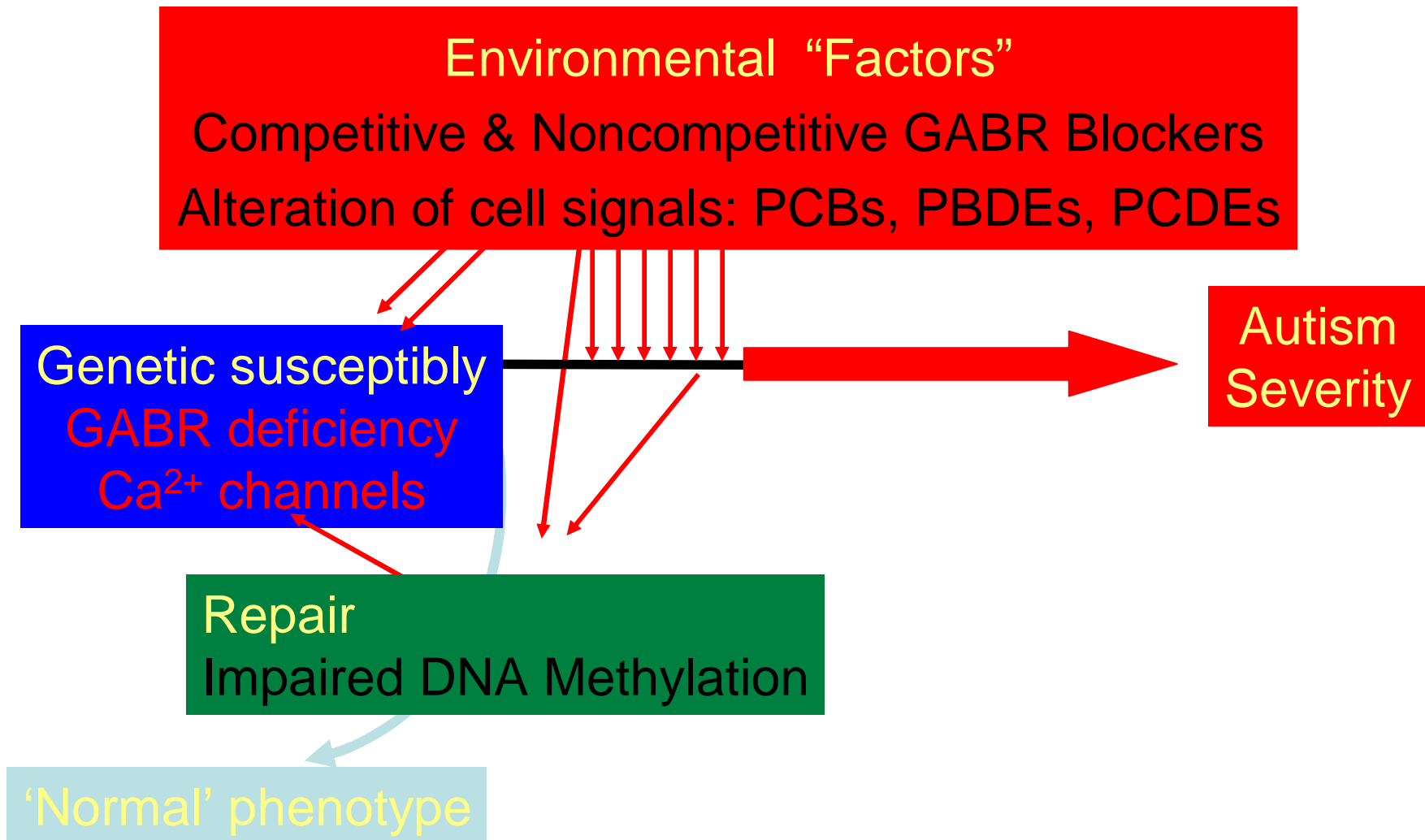
Framework for Future Studies

Mechanistic approaches are needed to understand gene-environment interactions in autism susceptibility



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Framework for Future Studies

What We Need

Humans

Case-Control Epidemiologic studies that are designed with the power to identify gene-environment interactions

Studies investigating immunological susceptibilities

Studies investigating nutrition and autism

Molecular, cellular, and *in vivo* models

Mechanistic and behavioral studies that use low [subtoxic] focus on signaling systems known to be affected in autism

Redirect focus to environmentally important chemicals that lack or have poor dioxin-like activity

Studies that focus on immune-neurodevelopment connection

Nutrition-based models