Rationale for Basic Science Component of CIFASD

- Inform clinical studies with basic molecular and animal data on FASD
  - Conditioned eyeblink response
  - Biomarkers of risk for FASD (5-HT, polymorphisms of kinases etc)
  - Developmental findings
- Development of agents that might prevent FASD in mothers who continue to drink
- Better understanding of pathophysiology may produce more targeted treatments of FASD.

Understand the Pathogenesis of FASD

- More informed search for behavioral and morphological phenotypic markers of FASD to improve the rapidity, sensitivity, and accuracy of diagnosis.
- Identify genetic and environmental factors that modify the risk of FASD.
- Clearer understanding of pathophysiology of FASD may produce more targeted prevention, intervention, and treatment.

Identification of a Behavioral Phenotype in FASD

- Are common behavioral abnormalities evident across animal species?
- Can specific behavioral abnormalities found in animals be identified in humans?
  - Conditioned eye blink
- Can candidate phenotypic behaviors in humans be reproduced and refined in animal models?

Characterization of the Biological Phenotype in FASD

- Can preclinical studies identify morphological or biological abnormalities that can be sought in humans?
  - Markers of nutritional deficiency
  - Markers of oxidative stress
  - HPA axis function and stress response
  - Neurotransmitter deficiency (eg. 5-HT, beta endorphin)
  - Immune response
  - Circadian rhythms
  - Peripheral nerve function.

- Can morphological or biological abnormalities identified in humans be reproduced in animal models to validate their specificity and determine their pathogenesis?
  - Interaction of ethanol neurotoxicity and nutritional deficiency

Prevention of FASD

- Identification of gene polymorphisms that predispose to FASD
  - Alcohol metabolizing enzymes
  - Enzymes involved in the metabolism or transduction of signals by critical neurotransmitters and growth factors.
  - Kinases that modify ethanol sensitivity

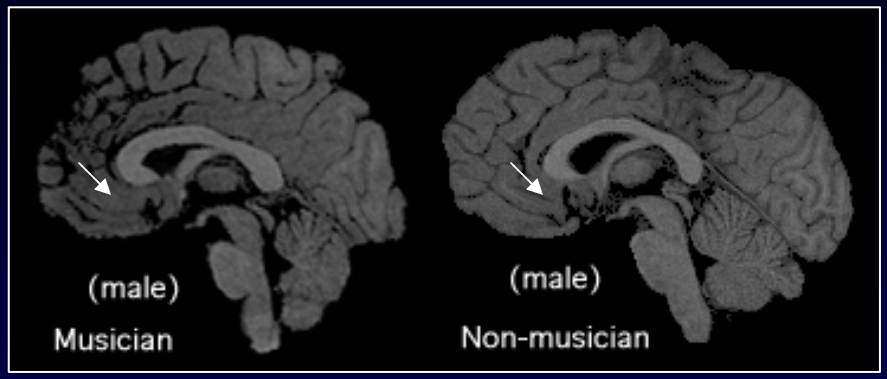
- Identification and correction of environmental factors that increase the risk of FASD
  - Deficiency of calories, vitamins, trace elements

- Development of specific ethanol antagonists that might be targeted to high risk mothers who are unable to stop drinking.
  - NAP, SAL
  - Antioxidants
  - 5-HT agonists

Treatment of FASD

- Biological Interventions
  - Choline
  - NAP
- General behavioral interventions
  - Environmental enrichment
- Targeted behavioral interventions
  - Motor learning (group music instruction)
- Social interventions.

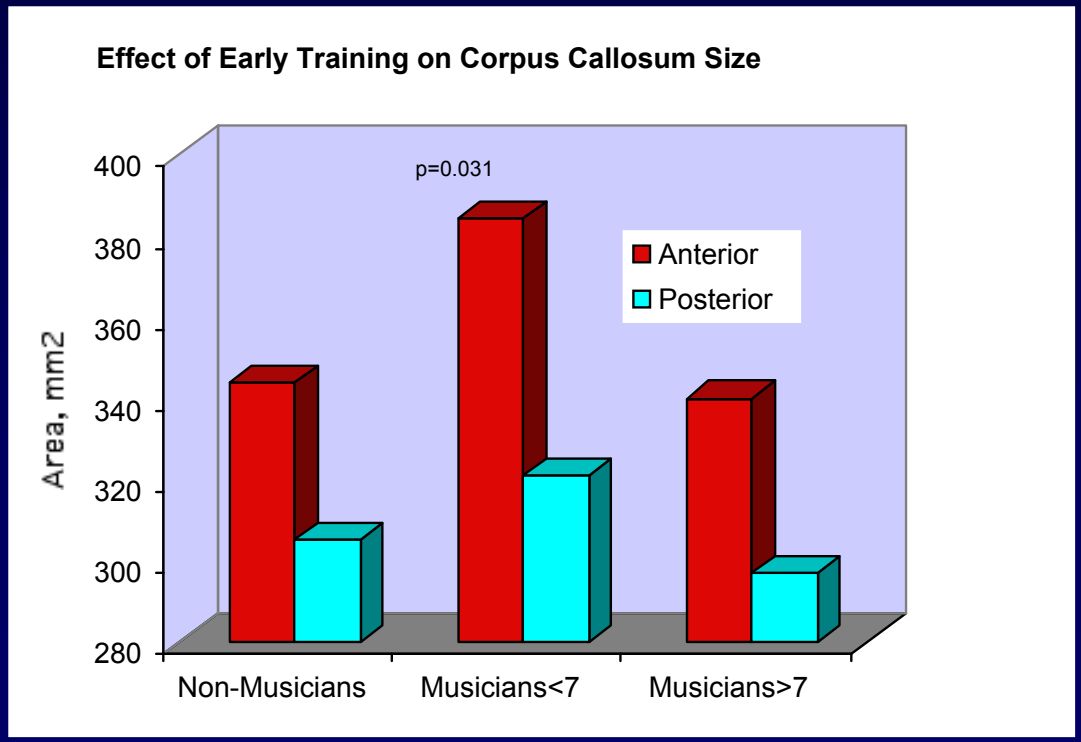
Enlargement of the corpus callosum in musicians with early training

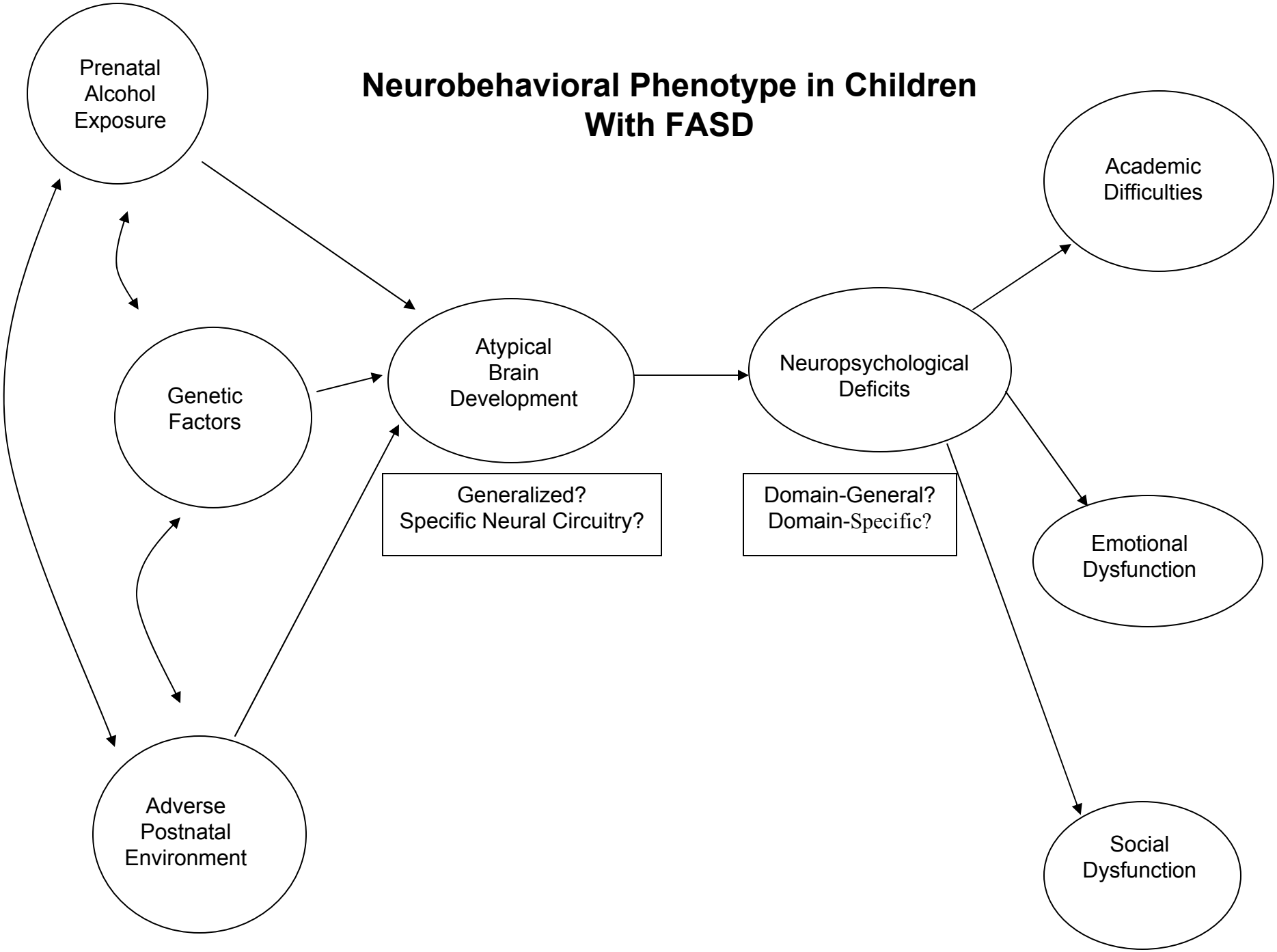


Mid-sagittal section of the corpus callosum in a musician and a non-musician. The corpus callosum of the musician is larger, particularly in the anterior part.

The anterior half of the corpus callosum is larger in a group of 21 musicians who began musical training under the age of 7 than in 9 musicians who began over the age of 7 or in 30 non-musicians.

Schlaug G, Jancke L, Huang Y, Staiger JF, Steinmetz H. Neuropsychologia 1995;33:1047




Neurobehavioral Phenotype in Children With FASD
Prenatal Alcohol Exposure
Genetic Factors
Adverse Postnatal Environment
Atypical Brain Development
Generalized? Specific Neural Circuitry?
Neuropsychological Deficits
Domain-General? Domain-Specific?
Academic Difficulties
Emotional Dysfunction
Social Dysfunction

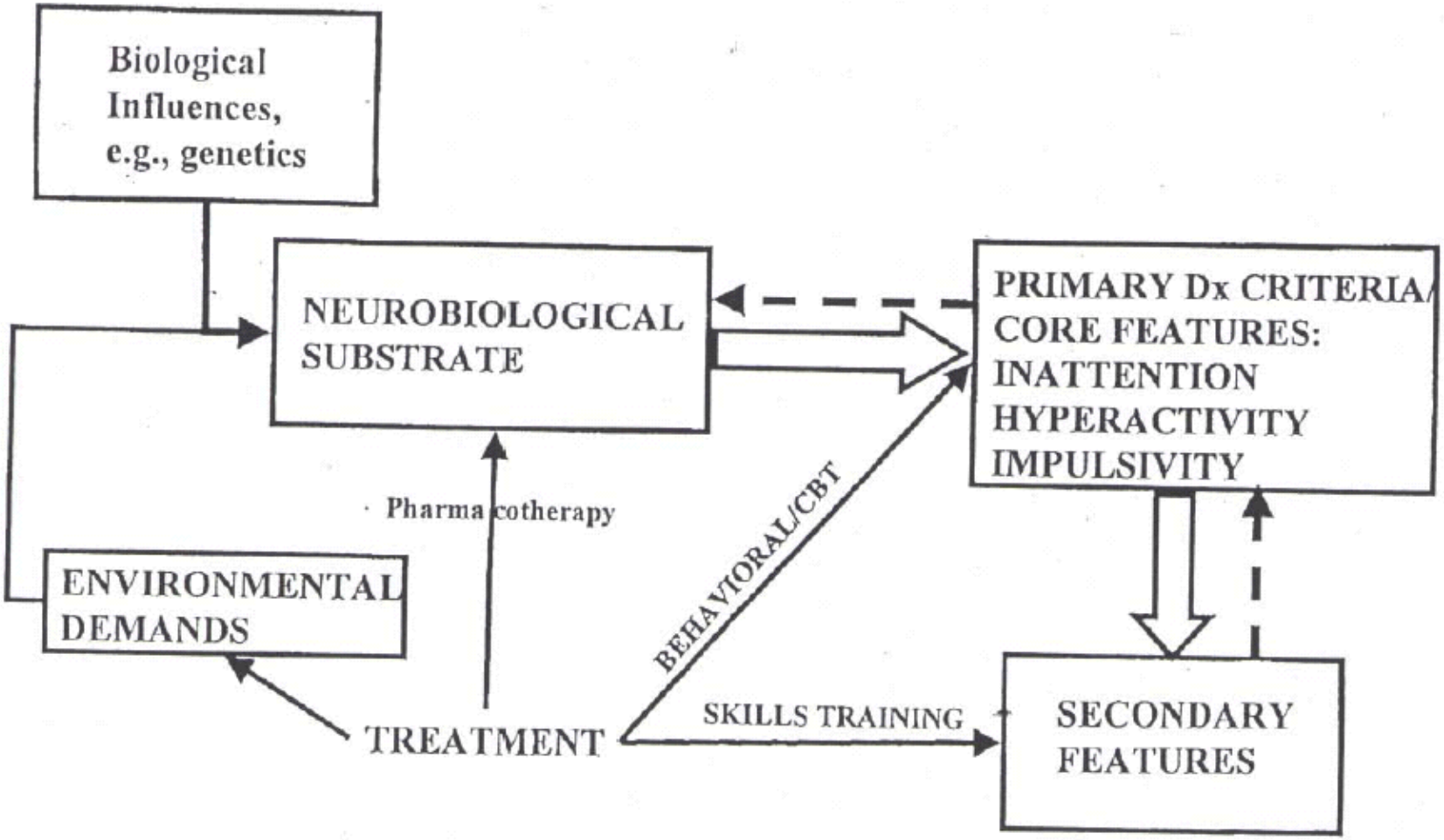


Figure 1. A conceptual model of child psychopathology.

Connections with Basic Sciences

- Selection of target areas – What aspects of an enriched environment contribute to the changes in the brain?
- Outcomes- Can we demonstrate the effects of interventions by neuroimaging or any other bio indexes?
- Mechanisms: What neurochemical mechanisms mediate behavioral outcomes?