


Integrating Molecular Genetics with Prevention

Joan Kaufman, Ph.D.

**Yale University School of Medicine
Department of Psychiatry
Child and Adolescent Research and Education
(CARE) Program**



Adoption and Safe Families Act P.L. 105-89

GOAL: Promote permanency for maltreated children in out-of-home care.

Permanency can be attained via:

- 1 – Reunification with birth families.**
- 2 - Adoption.**
- 3 - Guardianship granted to kin.**

Data Promoting the Passing of P.L. 105-89

- **Average length of stay in foster care estimated at 2 years.**
- **One-third of children in care spend the majority of their lives in “foster-care drift”.**
- **Time to permanency/adoption drawn out:**
 - **3-4 years from placement to filing for TPR.**
 - **1-2 years from filing to TPR ruling.**
 - **2-5 years to finalize appeals process.**

Promoting Permanence for Maltreated Children: The Connecticut Model

SAFE Homes Programs

- **Short-term group homes**
- **Community based**
- **Evaluation**
- **Treatment planning**



SAFE Homes: Retrospective Study

Subjects: 342 SAFE Home Cases

342 Traditional Foster Care Cases

First-time placements, 3-12 years of age at initial placement, propensity score matched cases from a larger cohort of 909 children.

Design: Longitudinal Record Review

Duration: 12-Month Follow-up

Child Abuse and Neglect, 2005

SAFE Homes: Retrospective Study

Primary Outcomes:

Number of out-of-home placements

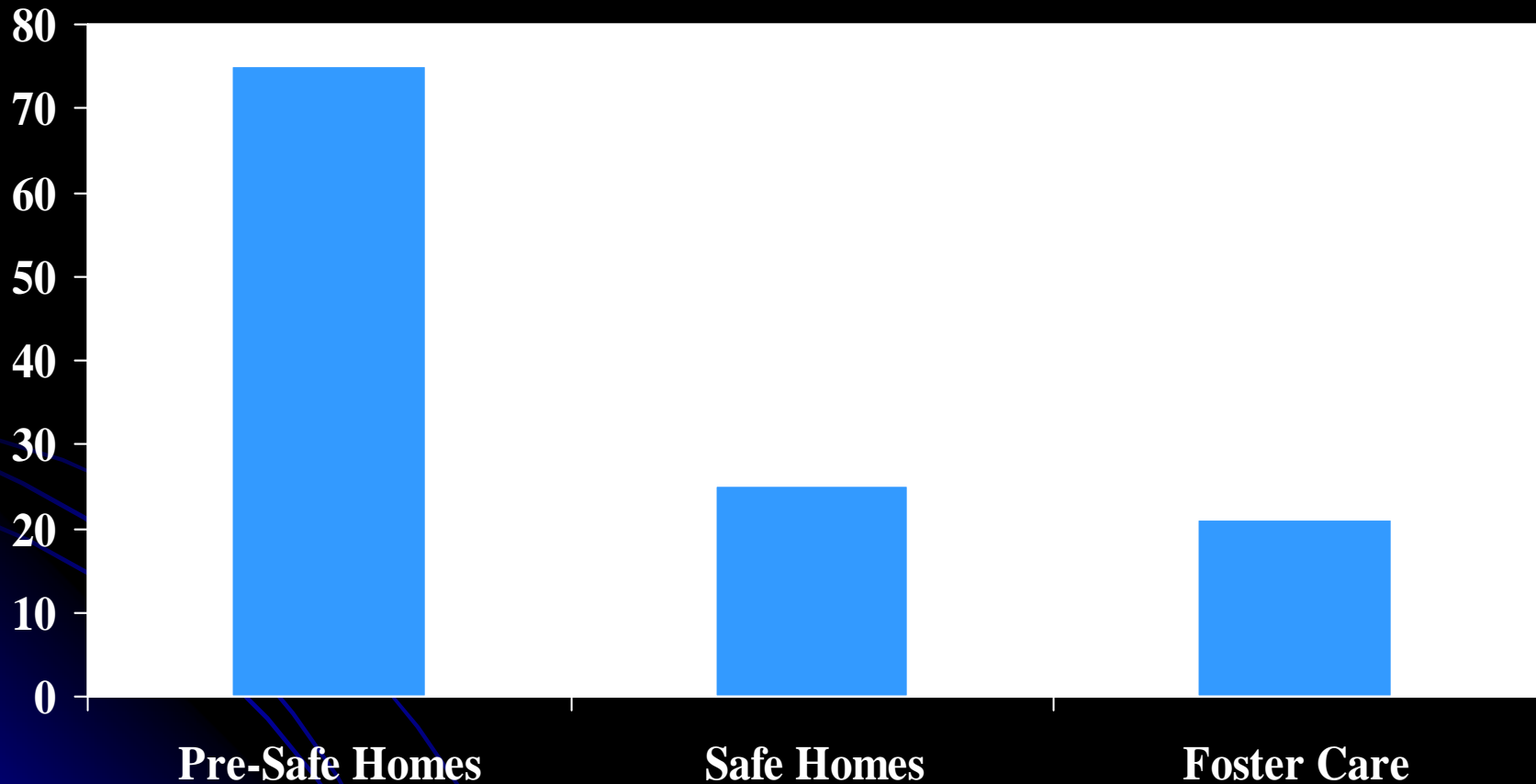
Duration in out-of-home care

Location at one-year follow-up

Placement with siblings/town of origin

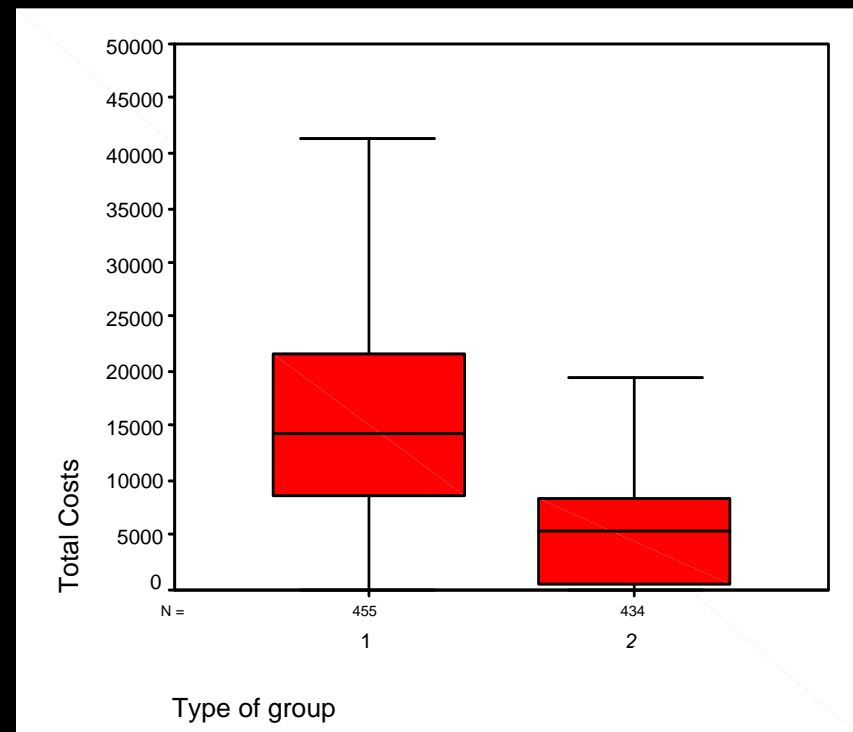
Cost of out-of-home placements

Proportion of Children with More Than 3 Placements in 12 Months




Cost for Out-of-Home Care

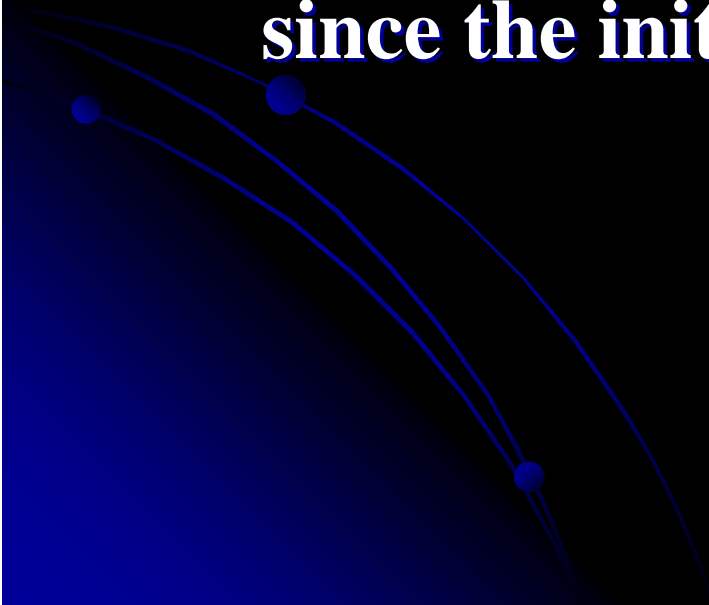
While the SH and FC children spent a comparable time in placement, the total cost for the out-of-home care of the children who were originally placed in the SAFE Homes was twice the total out-of-home care expenditures of the children who went to traditional foster care



Conclusions: Retrospective Study

- **Children are experiencing fewer placements in out-of-home care.**
 - **Improvement in outcome observed in SAFE Homes and Foster Care cases.**
 - **Changes appear due to a paradigmatic shift in practice.**
- 

Unanswered Questions:

1. **SAFE Homes: Is it Worth the Cost?**
 2. **Are children and families doing better since the initiation of SAFE Homes?**
- 

Prospective Longitudinal Two-Year Follow-Up Study of Children Participating in SAFE Homes

Department of
Children and Families

together with

Yale University's
C.A.R.E. Program

requests a moment of
your time...



- **Child well being, maltreatment, and placement data**
- **Study within a study -- examination of genetic and environmental risk and protective factors associated with a wide range of child outcomes.**
- **Assessments in Day Camp set up specifically for research purposes.**



SAFE Homes Summary:

- **The majority of children who enter out-of-home care have extensive histories with DCF.**
- **Almost 20% of the children experienced a new substantiated report of maltreatment during the one-year follow-up --- over 40% had one by the two-year follow-up.**
- **Approximately one in four children who were returned home re-entered care within 12-months.**
- **Untreated substance abuse and domestic violence problems were associated with high rates of re-abuse and prolonged time in care.**
- **By two-year follow-up, approximately half of the children were living in non-permanent placements.**



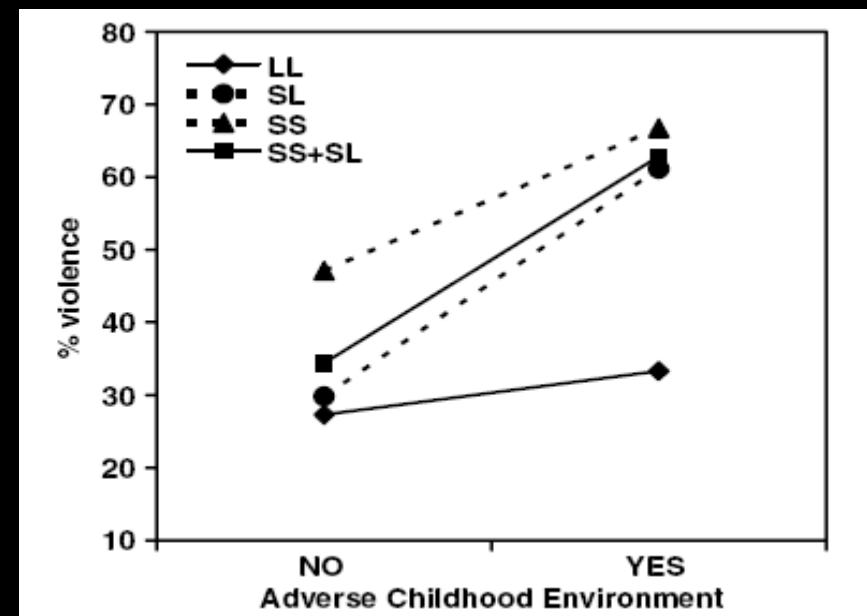
**Genetic and Environmental
Predictors of Aggressive Behaviors
in Maltreated Children
One-Year After Entry into
Out-of-Home Care**



Preliminary Analyses

Serotonin Transporter Genotype, Childhood Adversity, and Impulsive Aggression

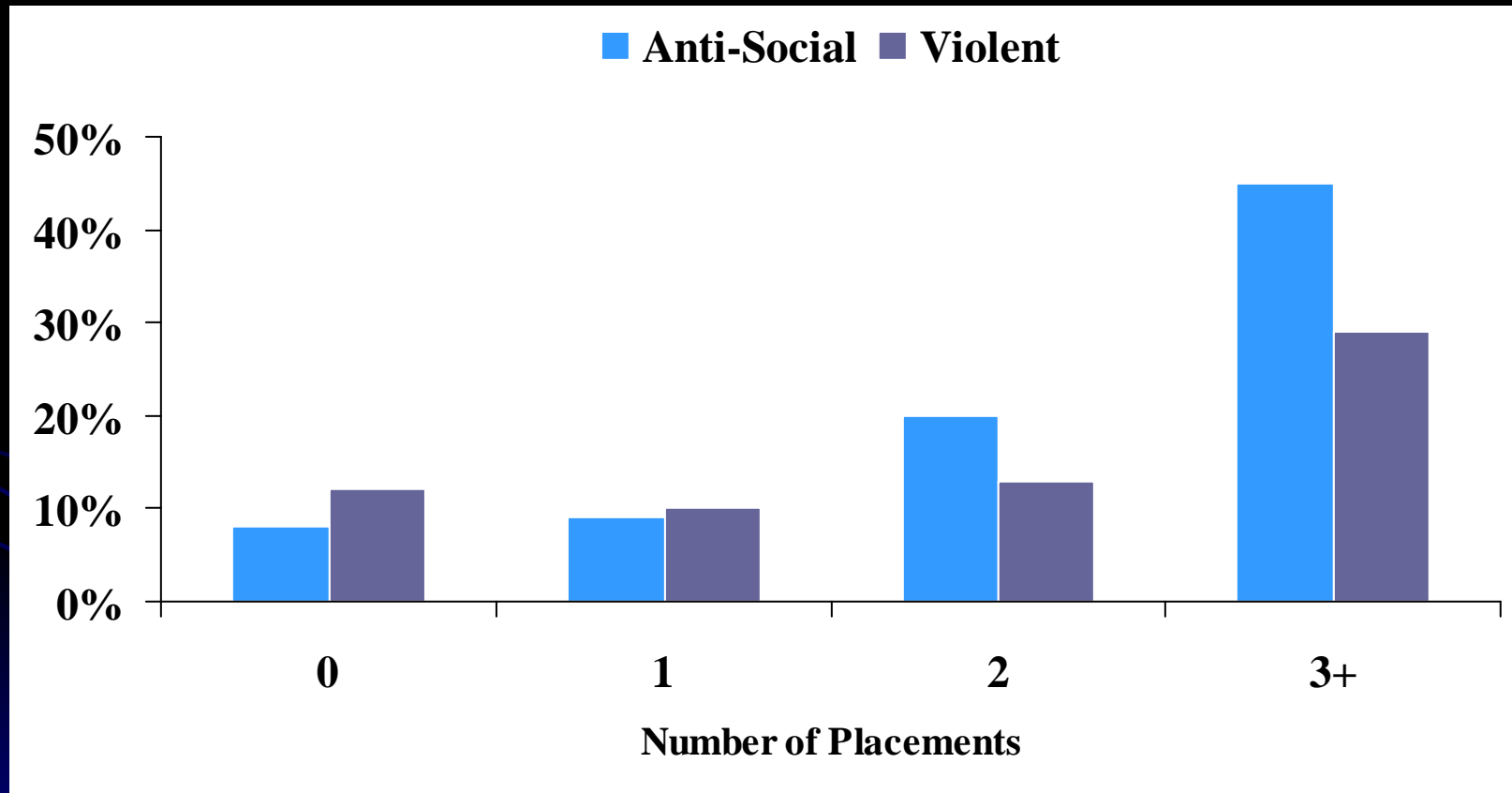
It is believed that the propensity for impulsive aggression, which is relatively unplanned and spontaneous but often culminates in physical violence, is associated with a low threshold for activating negative affect and with a failure to respond appropriately to the anticipated harmful consequences of behaving aggressively.



Reif et al. 2007

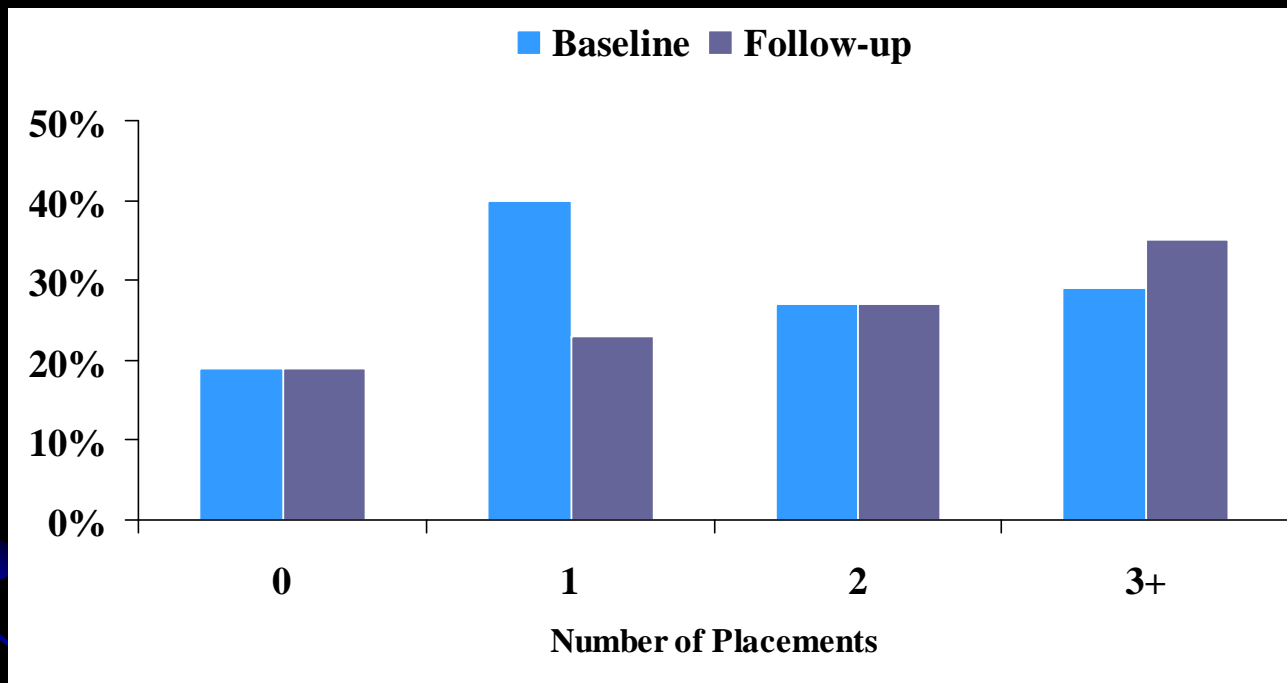
Placement History

Antisocial Behavior and Violence



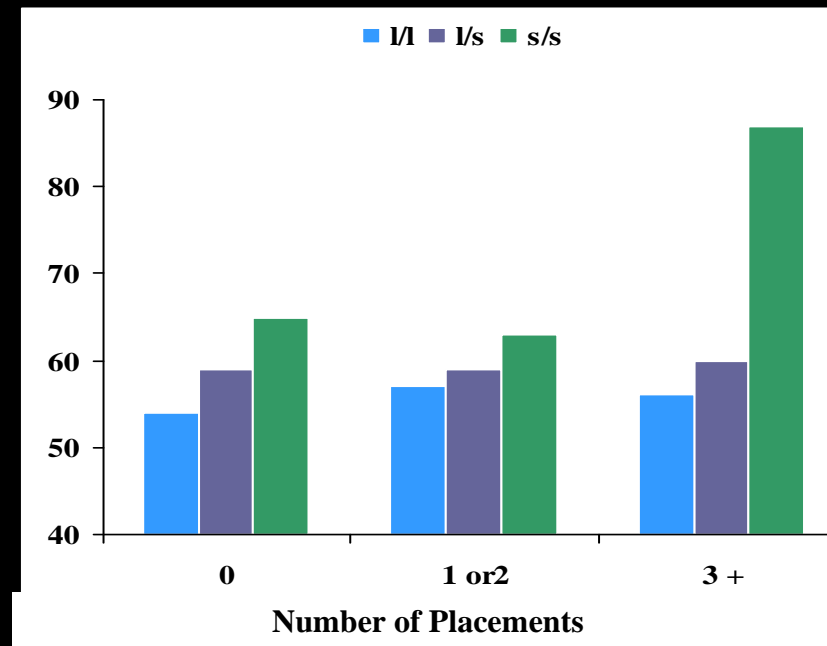
Widom et al., 1991

Predictors of Aggression at One-Year Follow-Up



Baseline Aggression Does Not Predict Number of Placements, but number of placements does predict aggression scores at follow-up.

Predictors of Aggression at One-Year Follow-Up



Significant Predictors: 1) Baseline Aggression Ratings; 2) Serotonin Transporter Genotype; 3) Number of placements; 4) Placement with siblings

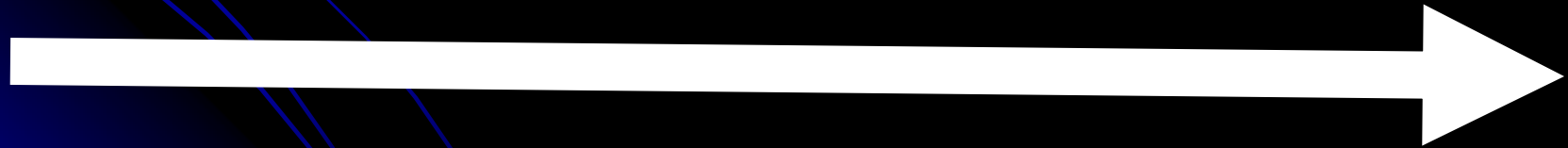
Opportunities for Prevention

Child Abuse Prevention
Olds et al.

**Substance Abuse/
Domestic Violence Tx**

Placement With Siblings

Prevention of Placement Disruption



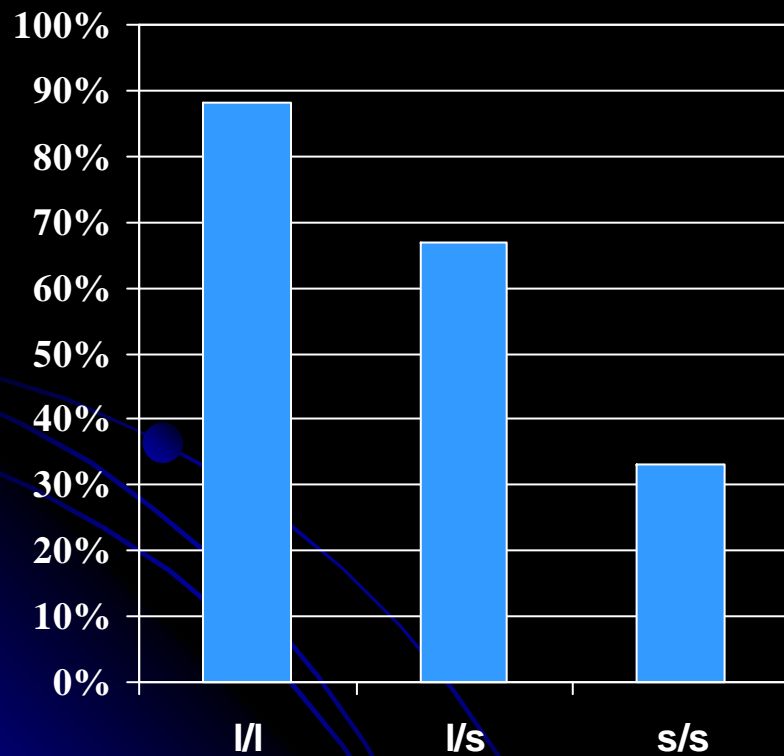
Maltreatment

Placement

Sociopathy

5-HTTLPR and Medication Response

Treatment x 5-HTTLPR Genotype



Stein et al., 2006

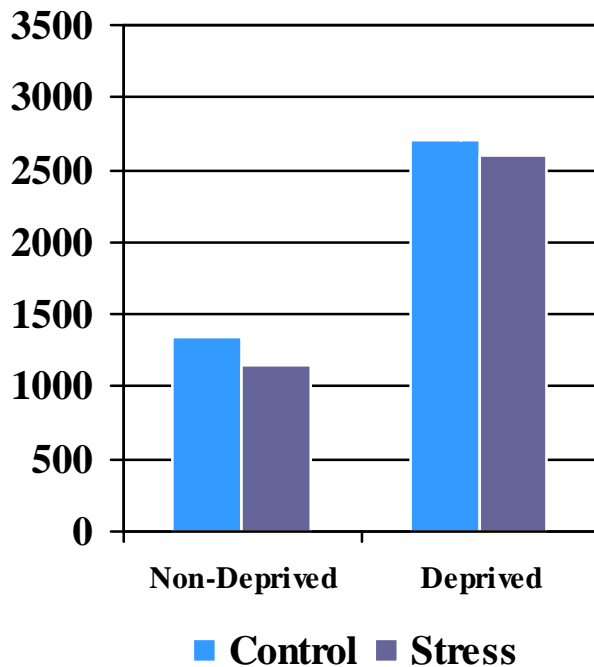
- Multiple small scale studies find association between 5-HTTLPR and treatment response
- Recent failure to replicate finding in large clinical trial (e.g., Kraft et al., 2007)
- In other disciplines, integrating genotype into treatment decisions has led to much improved outcomes.

Translational Research Approach

Central Tenet: Preclinical (e.g., animal) studies – especially studies on the effects of early stress – can help to guide hypotheses about the causes, prevention, and treatment of depression, PTSD and other stress related psychiatric illnesses.

Early Stress associated with long-term changes in stress reactivity and brain development

CRH in Adult Rats Stressed as Infants

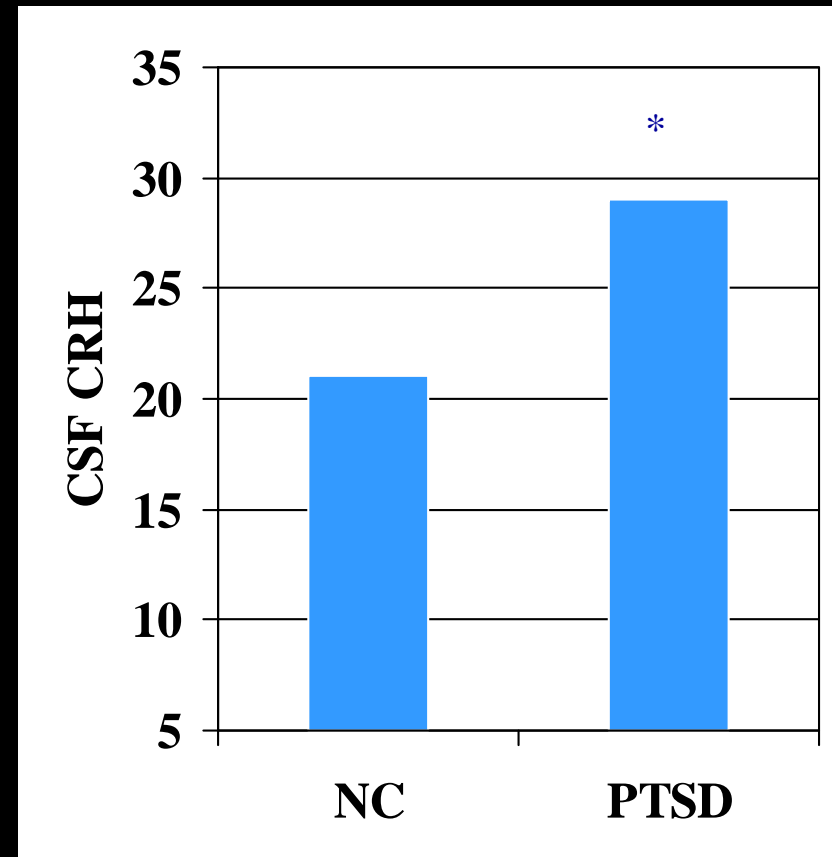


Maternal separation in infancy is associated in *adulthood* with:

- Increased basal and stress induced ACTH and corticosterone
- Increased CRH and NE drive in the hypothalamus, amygdala, and locus coeruleus
- Reduced tone of the GABA/BZ inhibitory system
- Multiple changes in the serotonergic system
- Hippocampal atrophy

Many of the Neurobiological Changes Associated with Early Stress are Reported in Adults with MDD and PTSD

- Multiple HPA axis abnormalities
- Increased cerebrospinal fluid CRH and NE
- Decreased GABA/BZ receptor number and/or binding
- Multiple indicators of altered 5-HT function
- Hippocampal atrophy



Bremner et al., 1997

Limitations Translational Perspective

Much of the pre-clinical studies on the effects of stress have examined the long-term impact of early stress on *adult* animals, with the application of research findings from these preclinical studies somewhat limited in guiding clinical research on the effects of stress in children and adolescents.

Corpus Callosum in Prepubescent Primates subject to Early Stress

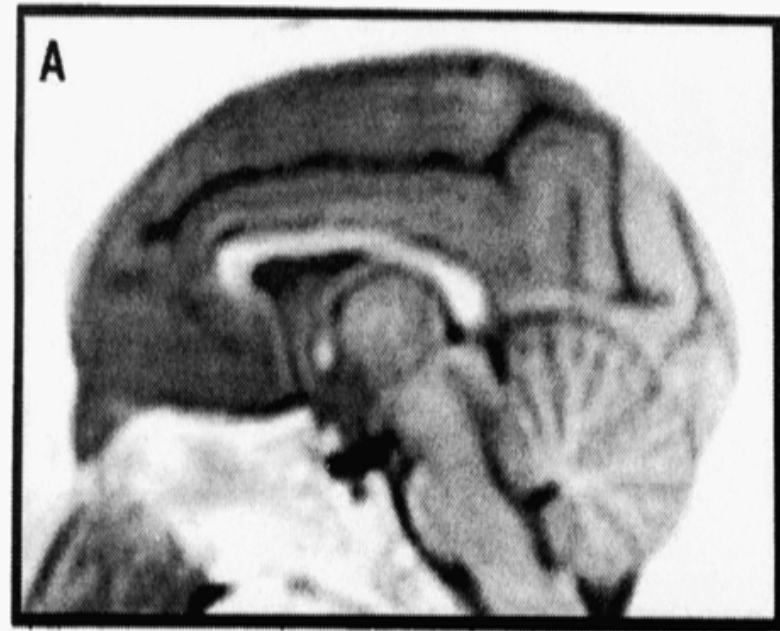
Sanchez et al. (1998)



- **Primates separated from their mothers during the first 3 weeks of life.**
- **Structural MRIs completed while prepubescents.**
- **Monkeys separated during infancy had reduced medial and caudal corpus callosum area.**
- **No evidence of hippocampal atrophy.**

Corpus Callosum in Maltreated Children with PTSD

- **DeBellis Study: 44 PTSD and 71 NC**
- **Children with PTSD had decreased area of the medial and caudal portions of the corpus callosum.**
- **No evidence of hippocampal atrophy.**
- **Replicated in three independent samples.**

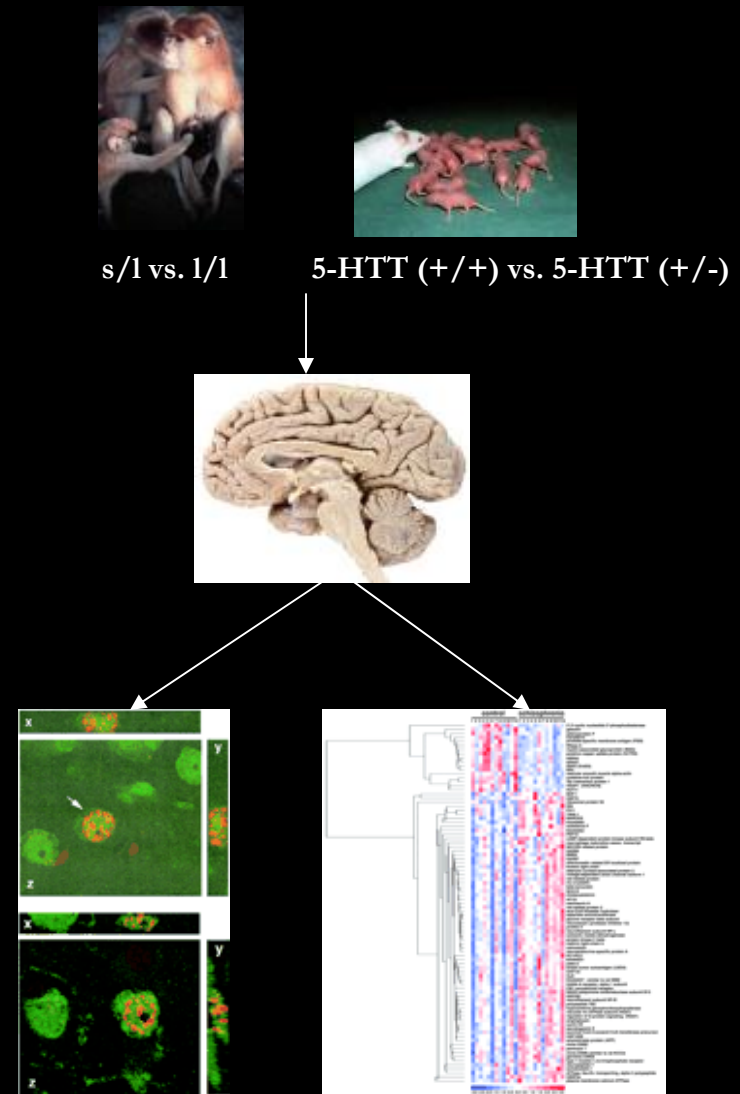


Formative Translational Center Application

Department of Health and Human Services Public Health Services Grant Application <i>Do not exceed character length restrictions indicated.</i>		LEAVE BLANK—FOR PHS USE ONLY.	
		Type	Activity
		Review Group	Number
		Council/Board (Month, Year)	Formerly
			Date Received
1.	TITLE OF PROJECT <i>(Do not exceed 81 Characters, including spaces and punctuation.</i> IDSC for the Study of Early Stress, Psycho	pathology, and Resilience in Children	
2.	RESPONSE TO SPECIFIC REQUEST FOR Number: PAR-06-062 Title: Interdisciplinary Develop	APPLICATIONS OR PROGRAM ANNOUNCEMENT mental Science Ctrs. For Mental Health	
Key Personnel Joan Kaufman, Ph.D. Director Ron Duman, Ph.D. Project PI Jeremy Coplan, M.D. Project PI Arie Kaffman, M.D., Ph.D. Investigator Sam Newton, Ph.D. Investigator Joel Gelernter, M.D. Investigator Andrew Dwork, Ph.D. Investigator Tarique Perera, M.D. Investigator		Other Key Contributors: John Krystal, M.D. Internal Advisory Board Jim Leckman, M.D. Internal Advisory Board Steve Southwick, M.D. Internal Advisory Board Pasco Rakic, M.D. Internal Advisory Board Michael Meaney, Ph.D. Consultant Hymie Anisman, Ph.D. Consultant Len Rosenblum, Ph.D. Consultant Harold Sacheim, Ph.D. Consultant	

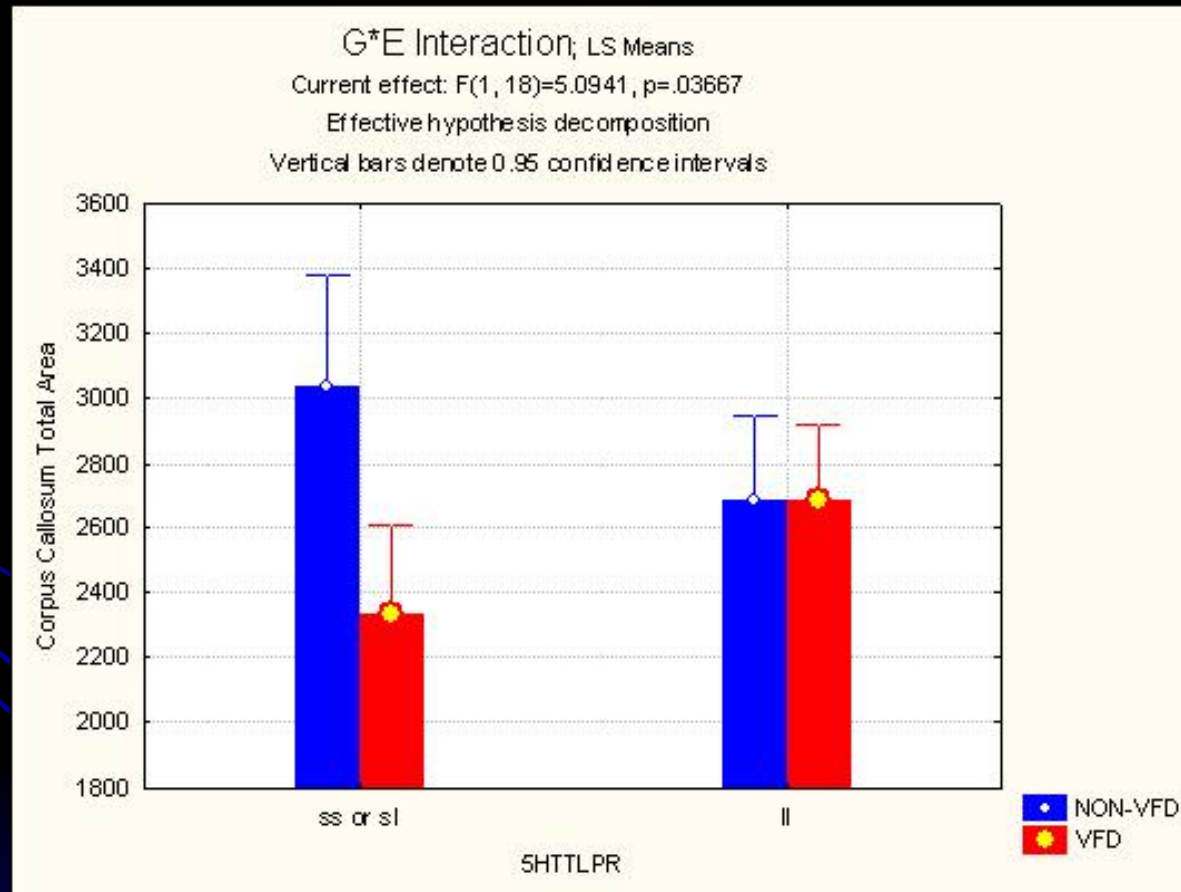
Translational Approaches to the Study of Early Stress, Psychopathology, and Resilience in Children

- **Rodent and primate models will be utilized to study the effects of genotype and early stress on brain development in prepubescent animals and across the lifecycle.**
- **Key Brain Regions: Corpus Callosum; Hippocampus**
- **Histological Studies of neural stem cell proliferation and differentiation of: 1) Neurons; 2) Oligodendrocytes**
- **Microarray Analyses: 1) Neurotrophic Factors and Signaling Factors; 2) Myelin-Related Genes**

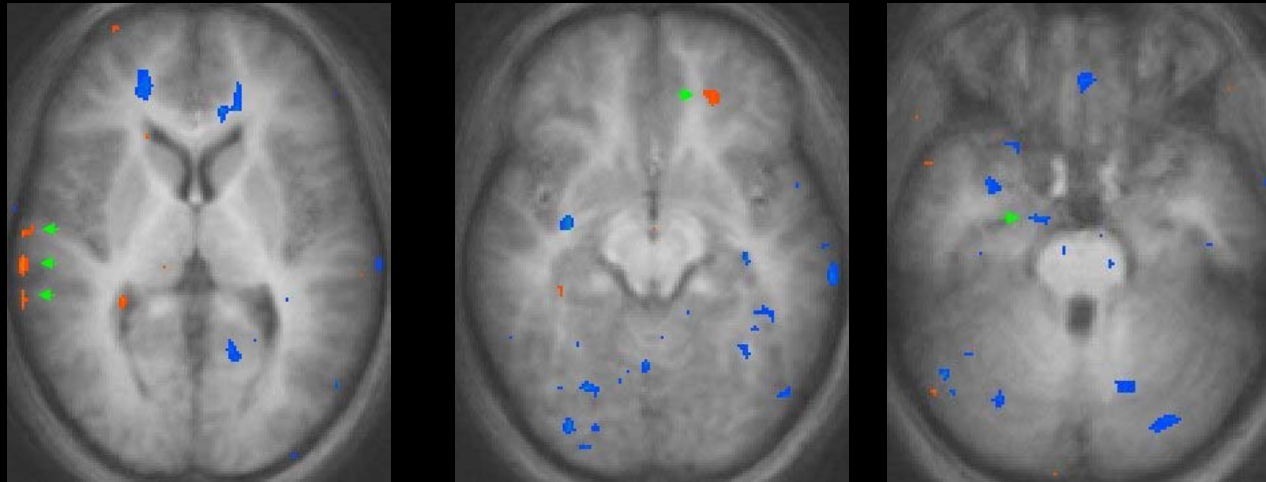


Primate Data: Preliminary G x E Findings

Predicting Corpus Callosum Area



fMRI Study of Dichotic Listening and Prosody Processing in Children



The dichotic listening paradigm we have selected requires interhemispheric transfer through posterior corpus callosum, and involves affective processing circuits which have been found to be disturbed in children and adults with depression and anxiety disorders, with key anatomical structures involved in these circuits sensitive to variation in 5-HTTLPR, environmental stress, and G x E interactions. This task also avoids racial biasing effects inherent in face processing tasks.

Conclusion

Better understanding of the neurobiological and psychosocial correlates associated with risk and resiliency in children will help to inform the development of more effective multi-modal interventions for children with histories of early trauma. It is our firm belief that the focus of clinical and research efforts for maltreated children must span from neurobiology to social policy.

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