Mechanisms underlying the intergenerational transmission of infant abuse in nonhuman primates

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The Intergenerational Transmission of Child Abuse

- In the U.S., approximately 800,000 children every year are maltreated, and in 75% of cases, maltreatment is perpetrated by the child's own parents
- If maltreated children are followed prospectively, 20-30% of them are likely to become abusive parents
- If abusive parents are investigated retrospectively, 70% of them report a history of early maltreatment
- Explanations for the intergenerational transmission of child abuse:
  - Abused children acquire the maltreatment behavior patterns through observational learning, modeling and reinforcement
  - Abused children acquire a particular cognitive model of the parent-child relationship, which will affect their parenting behavior
  - Early abuse results in long-term alterations in neuroendocrine development and emotion regulation, which may increase the probability of later abusive parenting

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EDITORIAL

SUPPOSE IT WERE A GENETIC DISORDER?

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PERIODICALLY OVER THE last several years, a number of us have speculated about what would happen if the problem of child abuse and neglect turned out to be a genetic disorder. The thought was scoffed at by those who know it is a "social" problem, but the thought (wish?) that there might be a genetic basis to child abuse and neglect still smolders. A recent article published in the July 26, 1996 issue of *Cell* has fanned the embers—so much so that serious consideration should now be given to funding basic genetic and neuroscience studies on the problem.

18. J. P. Saint-Jeannet, X. He, H. E. Varmus, I. B. Dawid, *Proc. Natl. Acad. Sci. U.S.A.* **94**, 13713 (1997).
19. C. Chang, A. Hemmati-Brivanlou, *Dev. Biol.* **194**, 129 (1998).
20. C. LaBonne, M. Bronner-Fraser, *Development* **125**, 2403 (1998).
21. M. A. Deardorff, C. Tan, J. P. Saint-Jeannet, P. S. Klein, *Development* **128**, 3655 (2001).
22. C. Tan *et al.*, *Development* **128**, 3665 (2001).
23. C. A. Cauthen, E. Berdougo, J. Sandler, L. W. Burrus, *Mech. Dev.* **104**, 133 (2001).
24. S. Hoppler, J. D. Brown, R. T. Moon, *Genes Dev.* **10**, 2805 (1996).
25. A. G. Bang, N. Papalopulu, M. D. Goulding, C. Kintner, *Dev. Biol.* **212**, 366 (1999).
26. L. L. McGrew, S. Hoppler, R. T. Moon, *Mech. Dev.* **69**, 105 (1997).
27. M. A. Nieto, M. G. Sargent, D. G. Wilkinson, J. Cooke, *Science* **264**, 835 (1994).
28. M. I. García-Castro, C. Marcelle, M. Bronner-Fraser, data not shown.
29. G. C. Tucker, H. Aoyama, M. Lipinski, T. Tursz, J. P. Thiery, *Cell Differ.* **14**, 223 (1984).
4767 (1998).
34. J. C. Hsieh *et al.*, *Nature* **398**, 431 (1999).
35. D. Cook *et al.*, *EMBO J.* **15**, 4526 (1996).
36. T. Yamada, S. L. Pfaff, T. Edlund, T. M. Jessell, *Cell* **73**, 673 (1993).
37. M. Hammerschmidt *et al.*, *Development* **123**, 95 (1996).
38. B. Neave, N. Holder, R. Patient, *Mech. Dev.* **62**, 183 (1997).
39. V. H. Nguyen *et al.*, *Dev. Biol.* **199**, 93 (1998).
40. V. H. Nguyen *et al.*, *Development* **127**, 1209 (2000).
41. D. J. Connolly, K. Patel, J. Cooke, *Int. J. Dev. Biol.* **41**, 389 (1997).
42. J. A. McMahon *et al.*, *Genes Dev.* **12**, 1438 (1998).
43. G. Winnier, M. Blessing, P. A. Labosky, B. L. Hogan, *Genes Dev.* **9**, 2105 (1995).
44. T. M. Schultheiss, J. B. Burch, A. B. Lassar, *Genes Dev.* **11**, 451 (1997).
45. D. Henrique *et al.*, *Nature* **375**, 787 (1995). The following probes were used: Slug [from A. Nieto (*16*)]; Wnts1, 3a, 4, 5a, 5b, and 6 (from A. McMahon); Wnt8c (from J. Dodd); BMP-4 (from D. Wu and P. Brickell); and BMP-7 (from M. Dickinson).
46. Intermediate neural plates from stage 10 [as described by V. Hamburger, H. L. Hamilton, *J. Morphol.*
strep control-CM, and Wg-CM were collected in 1/10 original volume. Wg (54 kD) was identified by Western blot analysis.
48. E. Pera, S. Stein, M. Kessel, *Development* **126**, 63 (1999).
49. A Hind III–Snc B1 fragment from mouse DnWnt1 [gift of R. Moon (*23*)] was cloned into a Hind III–Sma fragment of pC1 Neo (Promega, Madison, WI); permanently transfected 3T3 cells were selected after 3 months. Cell labeling and injections were performed [as described in (*10*, *11*)]. Expression of mRNA from DnWnt1 was detected after injection. Wnt1-cell lines were kindly provided by N. Brown and A. Kiespert.
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Role of Genotype in the Cycle of Violence in Maltreated Children

Avshalom Caspi,[1,2] Joseph McClay,[1] Terrie E. Moffitt,[1,2]* Jonathan Mill,[1] Judy Martin,[3] Ian W. Craig,[1] Alan Taylor,[1] Richie Poulton[3]

We studied a large sample of male children from birth to adulthood to determine why some children who are maltreated grow up to develop antisocial behavior, whereas others do not. A functional polymorphism in the gene encoding the neurotransmitter-metabolizing enzyme monoamine oxidase A (*MAOA*) was found to moderate the effect of maltreatment. Maltreated children with a genotype conferring high levels of *MAOA* expression were less likely to develop antisocial problems. These findings may partly explain why not all victims of maltreatment grow up to victimize others, and they provide epidemiological evidence that genotypes can moderate children's sensitivity to environmental insults.

Childhood maltreatment is a universal risk factor for antisocial behavior. Boys who experience abuse—and, more generally, those exposed to erratic, coercive, and punitive parenting—are at risk of developing conduct disorder, antisocial personality symptoms, and of becoming violent offenders (*1*, *2*). The earlier children experience maltreatment, the more likely they are to develop these problems (*3*). But there are large differences between children in their response to maltreatment. Although maltreatment increases the risk of later criminality by about 50%, most maltreated children do not become delinquents or adult criminals (*4*). The reason for this variability in response is largely unknown, but it may be that vulnerability to adversities is conditional, depending on genetic susceptibility factors (*5*, *6*). In this study, individual differences at a functional polymorphism in the promoter of the monoamine oxidase A (*MAOA*) gene were used to characterize genetic susceptibility to maltreatment and to test whether the *MAOA* gene modifies the influence of maltreatment on children's development of antisocial behavior.

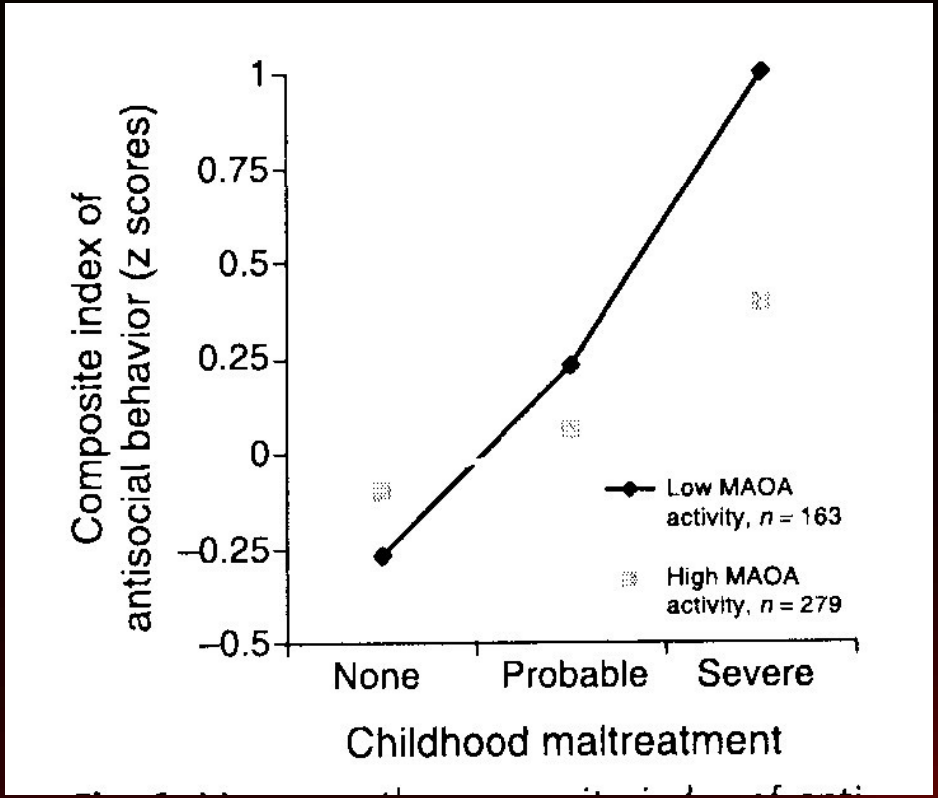
[1]Medical Research Council Social, Genetic, and Developmental Psychiatry Research Centre, Institute of

ing them inactive (*8*). Genetic deficiencies in *MAOA* activity have been linked with aggression in mice and humans (*9*). Increased aggression and increased levels of brain NE, 5-HT, and DA were observed in a transgenic mouse line in which the gene encoding *MAOA* was deleted (*10*), and aggression was normalized by restoring *MAOA* expression (*11*). In humans, a null allele at the *MAOA* locus was linked with male antisocial behavior in a Dutch kindred (*12*). Because *MAOA* is an X-linked gene, affected males with a single copy produced no *MAOA* enzyme—effectively, a human knockout. However, this mutation is extremely rare. Evidence for an association between *MAOA* and aggressive behavior in the human general population remains inconclusive (*13*–*16*).

Circumstantial evidence suggests the hypothesis that childhood maltreatment predisposes most strongly to adult violence among children whose *MAOA* is insufficient to constrain maltreatment-induced changes to neurotransmitter systems. Animal studies document that maltreatment stress (e.g., maternal deprivation, peer rearing) in early life alters NE, 5-HT, and DA neurotransmitter systems in ways that can persist into adulthood and can influence aggressive behaviors (*17*–*21*). In humans, altered NE and 5-HT activity is linked to aggressive behavior (*22*). Maltreatment has lasting neurochemical correlates in human children (*23*, *24*), and although no study has ascertained whether *MAOA* plays a role, it exerts an effect on all aforementioned neurotransmitter systems. Deficient *MAOA* activity may dispose the organ-

The monoamine oxydase A (MAOA) enzyme metabolizes the monoamine neurotransmitters serotonin, norepinephrine and dopamine

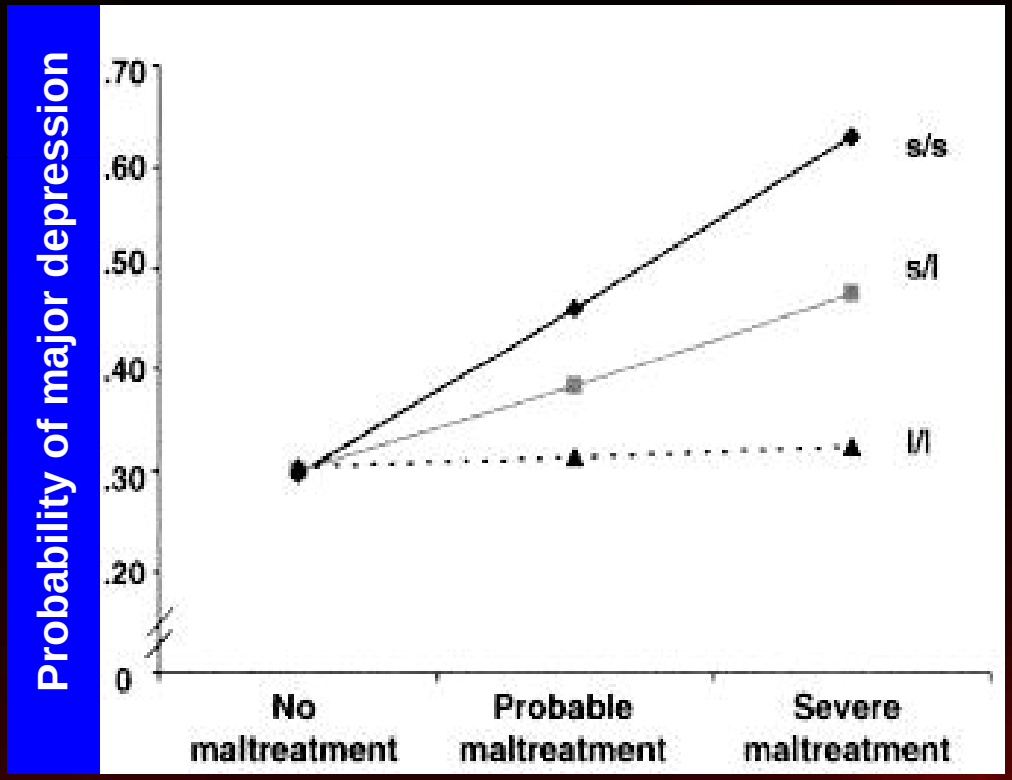
There is a functional polymorphism in the promoter region of the gene that encodes for the MAOA enzyme: a repetitive DNA sequence that occurs in two allelic variants associated with low and high MAOA activity



(Caspi et al. Science 2002)

The serotonin transporter (5HTT) gene polymorphism modulates the effects of early child maltreatment on later major depression

In the promoter region of the 5HTT there is a repetitive DNA sequence that occurs in two allelic variants, short (s) and long (l): the “s” allele variant confers lower transcriptional efficiency to the 5-HTT gene promoter



(Caspi et al., Science 2003)

These studies do not provide direct experimental evidence that child maltreatment is transmitted across generations;

And they do not elucidate the physiological mechanisms through which genotype and early experience affect the intergenerational transmission of child maltreatment.

Research with animal models can help us understand the relative contributions of biological and environmental factors (and the underlying mechanisms) to the long-term consequences of child maltreatment and its transmission across generations.

Infant abuse in rhesus monkeys

Subject Population

Site: The Field Station of the Yerkes National Primate Research Center, Lawrenceville, GA
Population: > 1,500 rhesus macaques
Housing: large multi-male multi-female social groups

INFANT ABUSE IN RHESUS MACAQUES:
General Characteristics

- 5-10% of all infants born in a given year are physically abused by their mothers. Infant sex, birth order, and health status do not affect the probability of occurrence of abuse.
- Information from over 3,000 individuals over a period of 5-7 generations has shown that infant abuse runs in families along the maternal line. It is concentrated in some matrilines and, within these matrilines, it is most likely to be exhibited by mothers, daughters, or sisters. The physical patterns of abuse tend to differ between matrilines.
- Abuse begins as early as the first day of infant life and usually ends by the time infants are 3 months old.
- Abusive behavior is limited to a female's own offspring.
- Abusive behavior is very different from any other pattern of maternal or aggressive behavior.
- Abusive behavior co-occurs with high rates of maternal rejection

INFANT ABUSE IN RHESUS MACAQUES:
The role of infant, mother, and surrounding environment

- Infants are abused as early as on their first day of life when they still show little or no independent activity.
- There are no obvious early differences in the physical and behavioral characteristics of abused and nonabused infants
- Abusive mothers abuse most, if not all, of their infants over the years and are consistent in both their rates and their patterns of abusive behavior across different infants
- Abusive mothers also abuse unrelated adopted infants with rates and patterns similar to those exhibited with their biological offspring
- Abuse appears to be a stable maternal characteristic
- Abusive mothers have high levels of anxiety/impulsivity
- Abusive mothers are more likely to carry the short 5-HTT allele
- Infant abuse is associated with social stress

Study 1: The role of genes and experience in the intergenerational transmission of infant abuse in rhesus monkeys: a cross-fostering experiment

4 experimental groups of subjects:

1) Female infants born to abusive mothers and reared by them (n=8)

2) Female infants born to control mothers but adopted and reared by abusive mothers (n=9)

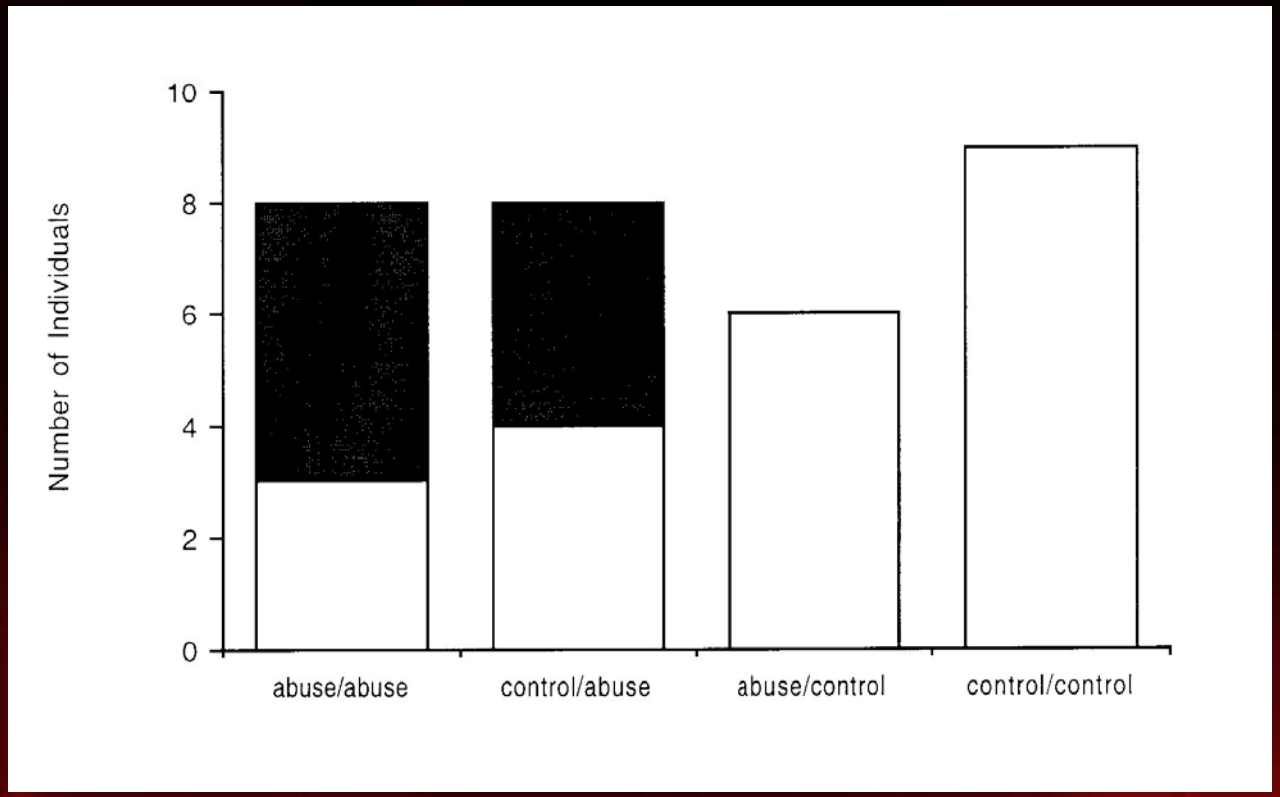
3) Female infants born to abusive mothers but adopted and reared by controls (n=7)

4) Female infants born to control mothers and reared by them (n= 8)

- Cross-fostering procedures took place within 24-48 hours after birth;
- The infants adopted and reared by abusive mothers were abused by them as if they had been their biological offspring;
- All female infants were followed for 4-5 years until they gave birth for the first time and their maternal behavior was studied.

Proportiion of individuals displaying abusive parenting in adulthood among:

1) Females born to abusive mothers and reared by them (abuse/abuse)
2) Females born to control mothers and reared by abusive mothers (control/abuse)
3) Females born to abusive mothers and reared by control mothers (abuse/control)
4) Females born to control mothers and reared by them (control/control)



(Maestripieri, PNAS, 2005)

Study 2: Neuroendocrine mechanisms underlying the effects of early experience: HPA axis and brain serotonin

Subjects:

- 43 infants reared by their biological mothers (22 abused, 21 controls)
- 16 infants reared by adoptive mothers (9 abused, 7 controls)

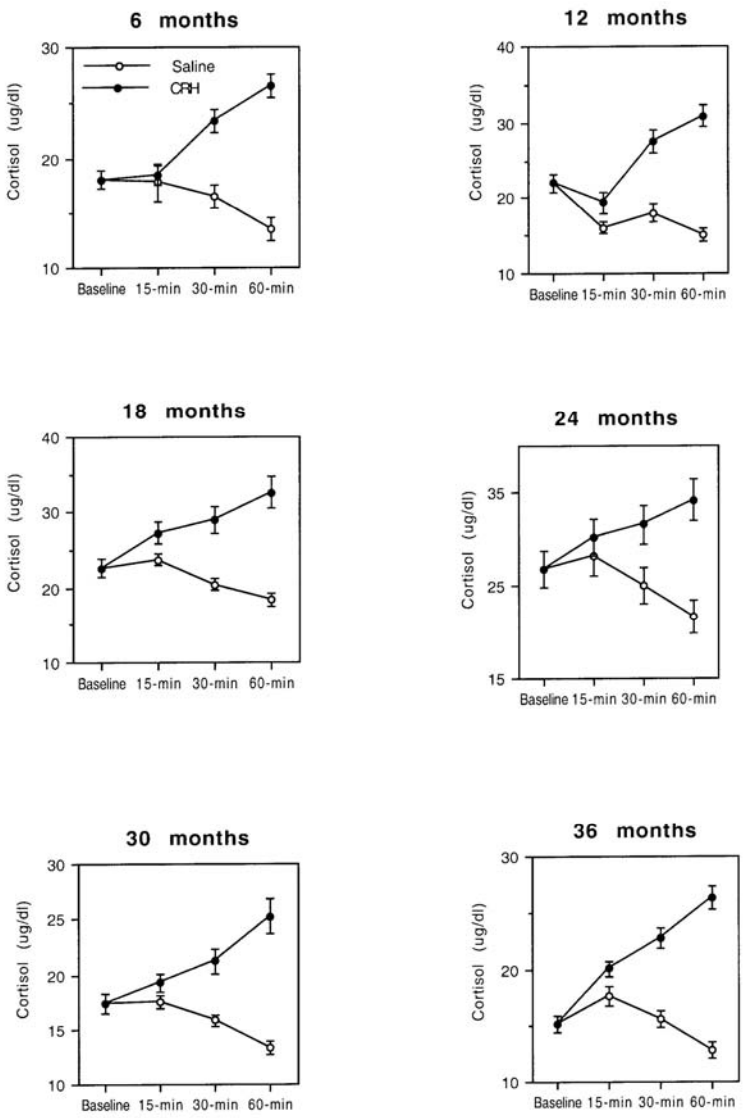
Measures

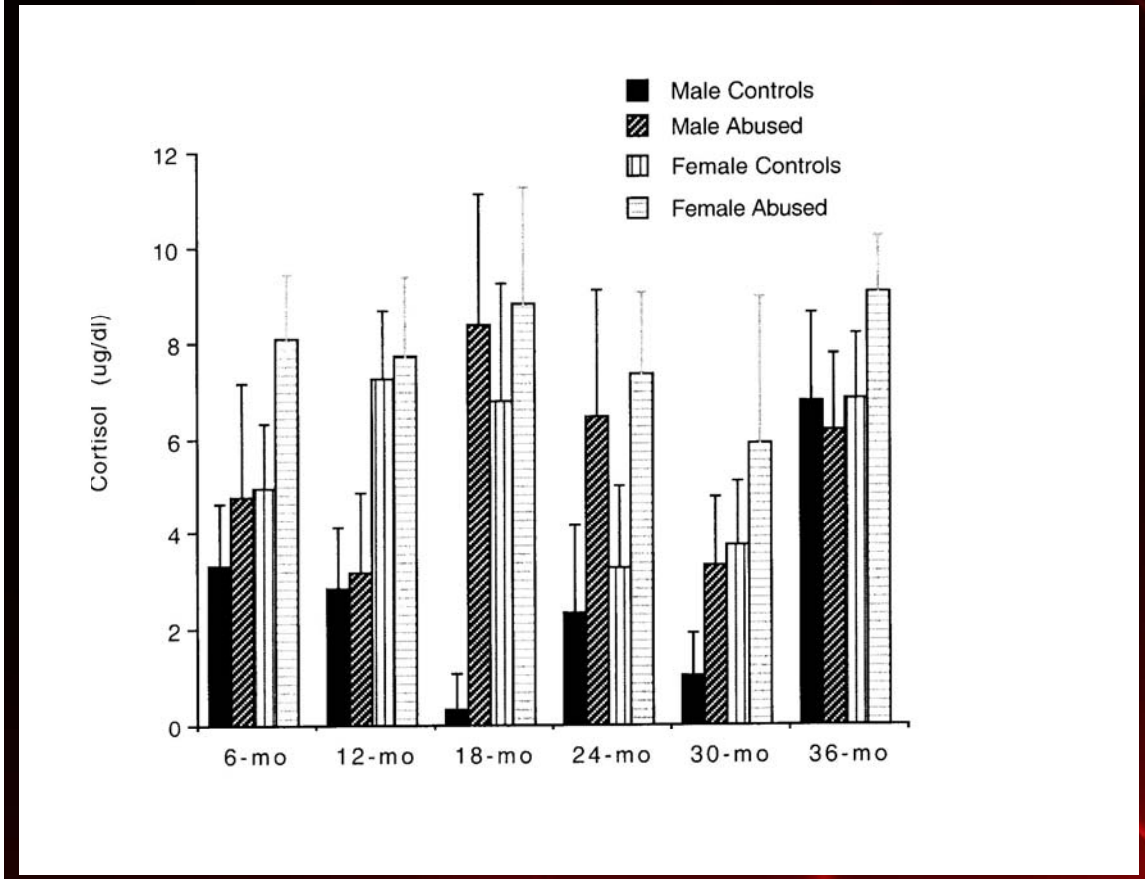
- Plasma cortisol responses to stress, CRH challenge, ACTH challenge, dexamethasone test at 6, 12, 18, 24, 30, 36 months of age
- CSF concentrations of serotonin metabolite 5-HIAA at 6, 12, 18, 24, 30, 36 months of age

Abusive behavior co-occurs with high rates of maternal rejection

- Strong effects of abuse on HPA axis
- Strong effects of rejection on 5-HIAA

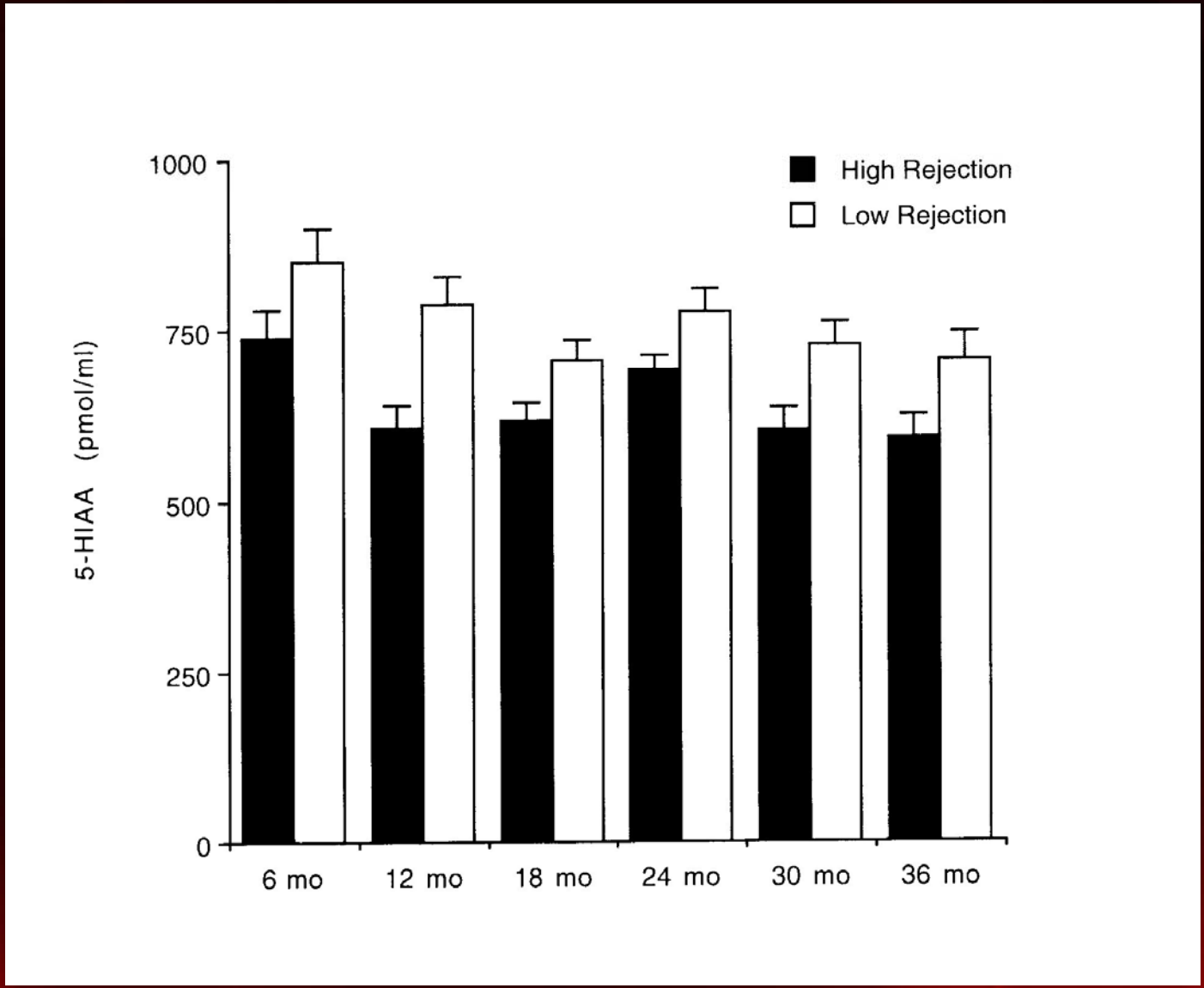
THE CRH CHALLENGE:
abused infants show consistently higher cortisol responses to CRH than controls at any age





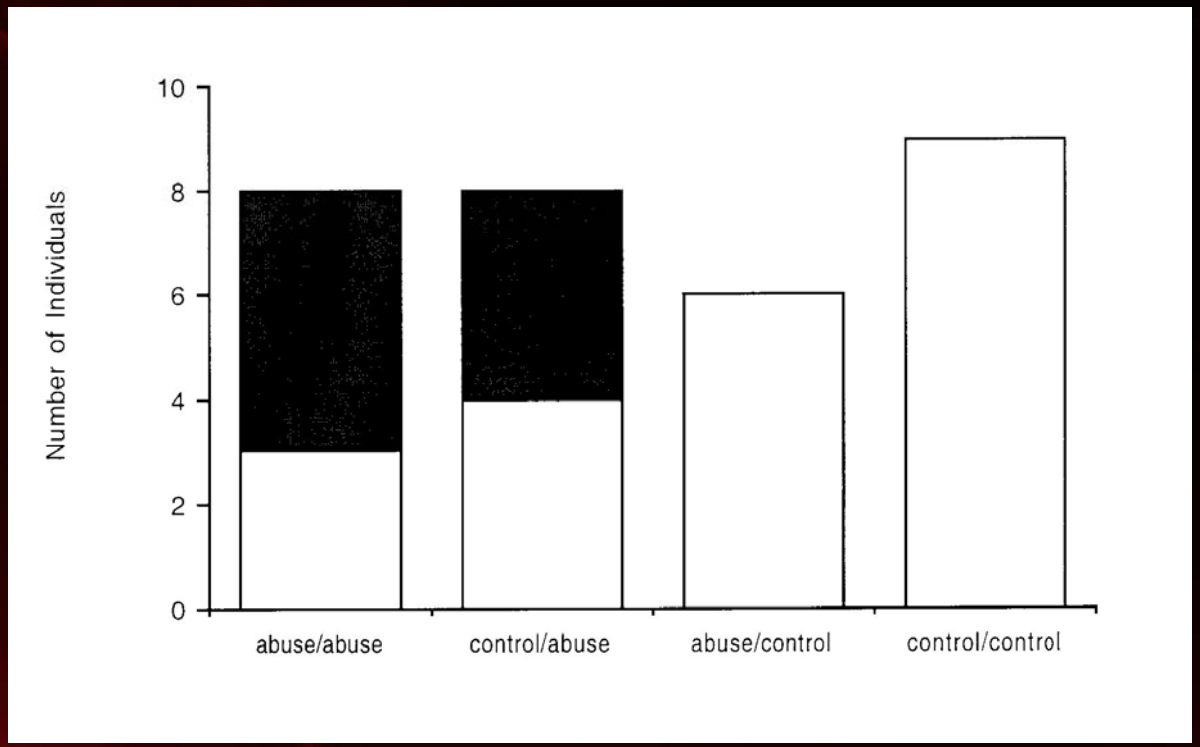
(Sanchez et al., Development & Psychopathology, 2010)

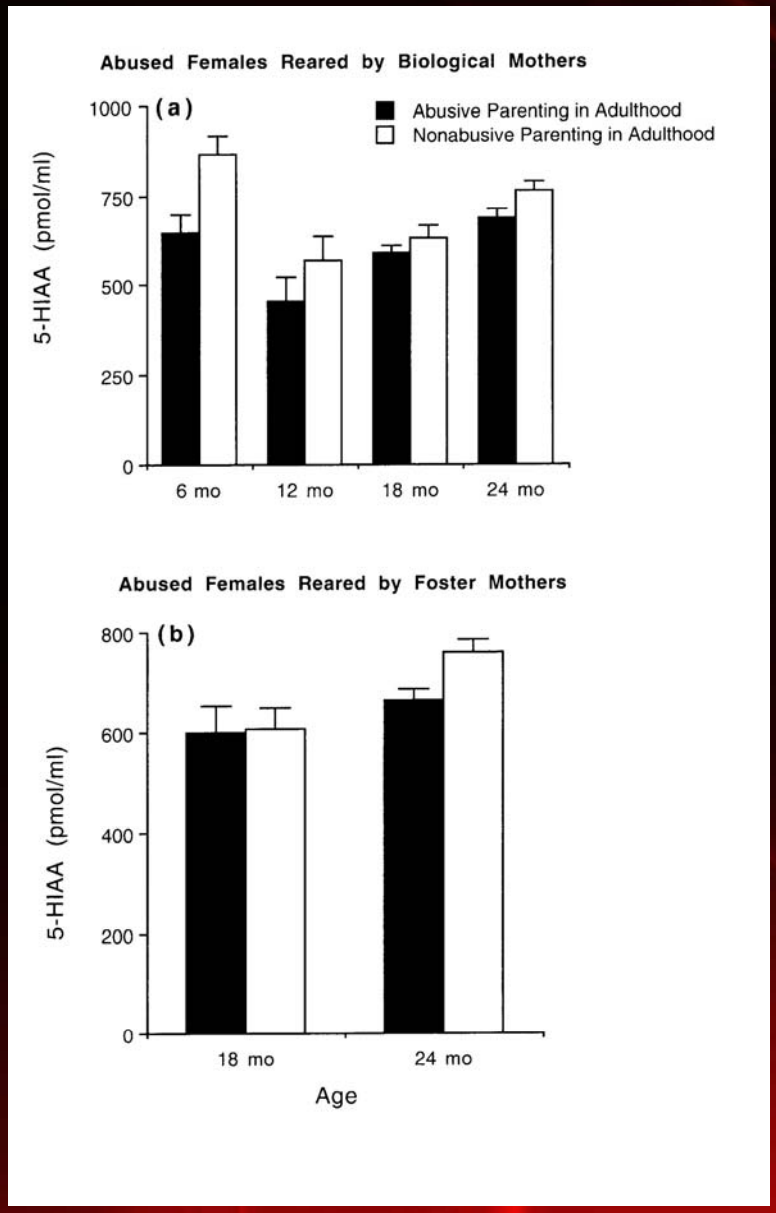
Infants exposed to high rates of maternal rejection show consistently lower CSF 5-HIAA than infants exposed to low rates of rejection (true for both infants reared by biological mothers and for cross-fostered infants)



(Maestripieri et al., Behavioral Neuroscience, 2006)

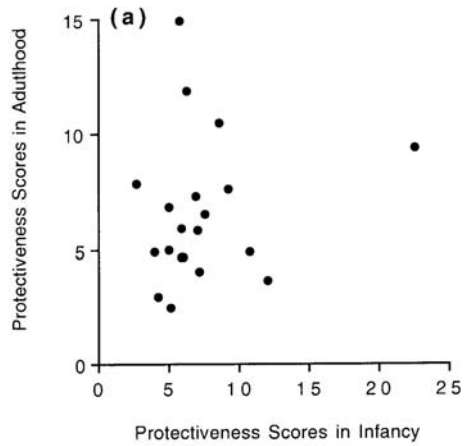
Abused females who become abusive mothers themselves have lower CSF 5-HIAA than abused females who don't become abusers

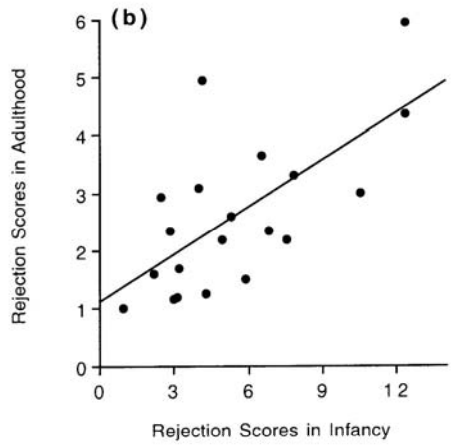




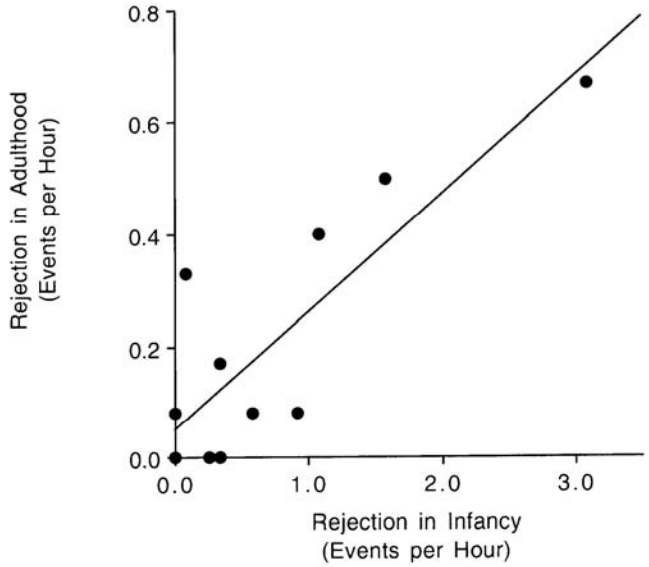
(Maestripieri et al., Behavioral Neuroscience, 2006)

Intergenerational transmission of maternal rejection: Maternal rejection rates in infancy and adulthood





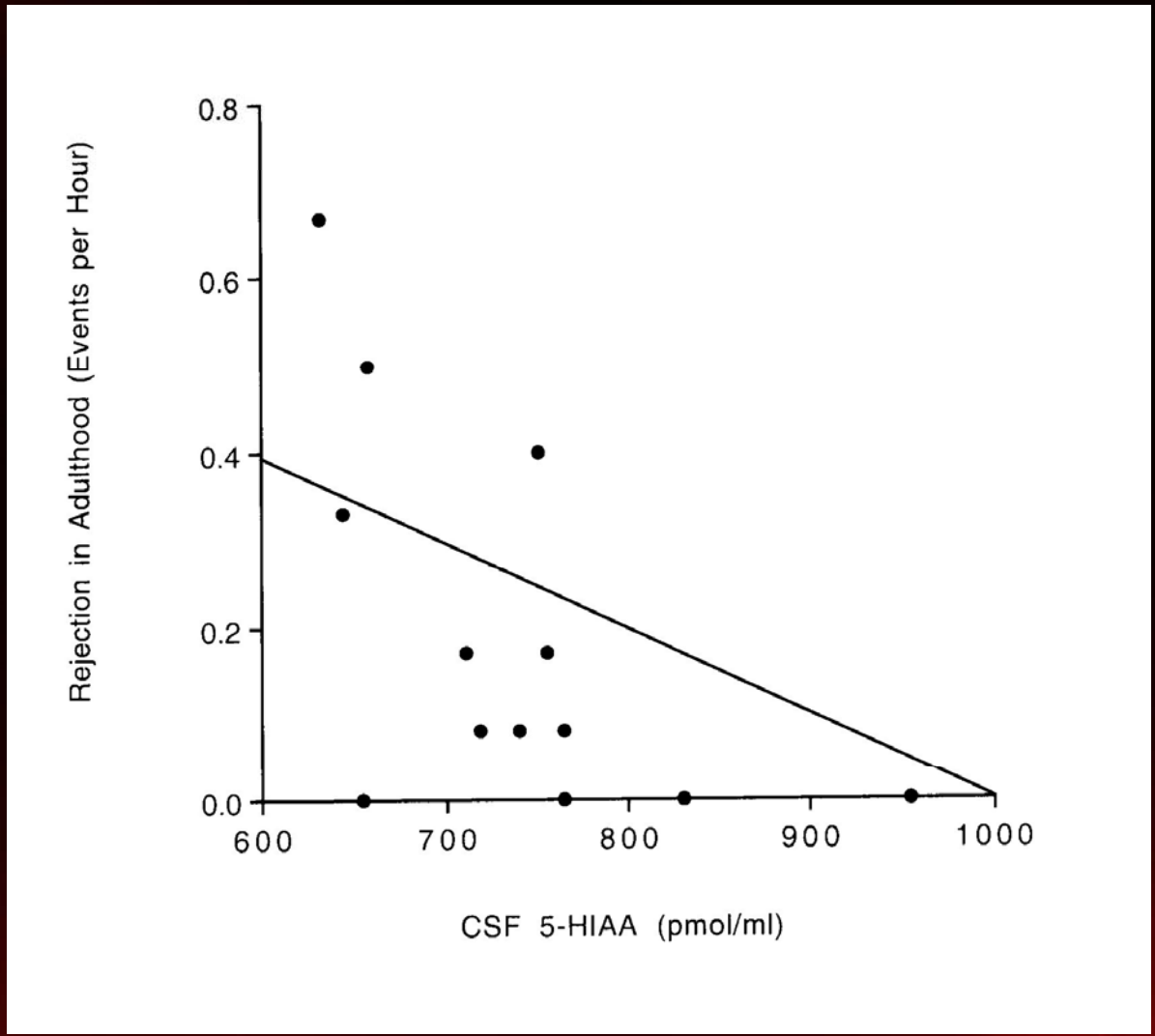
Cross-fostered + noncrossfostered



Cross-fostered females only

(Maestripieri et al., Developmental Psychobiology, 2007)

Intergenerational transmission of maternal behavior: CSF 5-HIAA correlates with maternal rejection rates of adult cross-fostered females



(Maestripieri et al., Developmental Psychobiology, 2007)

Other findings

- Abused infants show alterations in cortisol diurnal fluctuations early in life and greater cortisol response to stress (separation from mother) later in life
- Abuse-induced alterations of stress hormones are particularly pronounced in individuals who carry the short allele of the 5-HTT gene;
- Individuals with lower serotonergic activity and greater responsivity of stress hormones exhibit elevated anxiety and impulsive aggression

Summary and Conclusions

- Data from over 7 generations of rhesus monkeys indicate that infant abuse runs in families.
- Abusive mothers are likely to carry the short allele of the 5-HTT gene, suggesting that genetic factors may be implicated in the transmission of abuse.
- Infant cross-fostering experiments showed that early experience plays an important role in the transmission of abusive parenting and rejection behavior from mothers to daughters.
- Cross-fostered females who experienced high rates of maternal rejection and abuse in infancy exhibit lower CSF concentrations of 5-HIAA in the first 3 years of life;
- Females with lower CSF levels of 5-HIAA display high rates of maternal rejection in adulthood;
- Abused females who become abusive mothers themselves have lower CSF levels of 5-HIAA than abused females who don't become abusive mothers;
- Abused individuals show higher responsivity of stress hormones (HPA axis) later in life, particularly if they carry the short allele of the 5-HTT gene;
- Individuals with low serotonin function and hyperreactivity of the HPA axis exhibit high anxiety and impulsive aggression;
- Long-term alterations in the serotonergic system and in hormones of the HPA axis induced by early exposure to maternal abuse and frequent rejection contribute to the intergenerational transmission of maladaptive parenting, through mechanisms involving altered emotional reactivity and impulsivity.

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