

# **Disordini da uso di sostanze: dimensioni genetiche?**

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## Current Opinion in Psychiatry

# ANTECEDENTS of SUBSTANCE USE IN ADOLESCENCE

Poikolainen, 2002

- Difficult temperament
- Aggressiveness
- Impulsivity
- Conduct problems
- Poor intelligence
- Attachment to bad company
- Bad parenting

- 
- non-adaptive coping
  - social anxiety
  - mood disorders

TABELLA 5

	<b>PBI</b> Accudimento Paterno	<b>PBI</b> Accudimento Materno	<b>Zuckerman</b> Sensation Seeking	<b>BDHI</b> Aggressivita' Diretta	<b>EPQ</b> Maladattament Sociale
<b>Abstinent</b>	<b>25,49±0,42*</b>	<b>27,59±0,38*</b>	<b>15,96±0,29</b>	<b>3,01±0,14</b>	<b>2,69±0,11</b>
<b>Minimal experimenters</b>	<b>24,2±0,65*</b>	<b>27,0±0,56*</b>	<b>20,05±0,47*</b>	<b>4,18±0,47**</b>	<b>3,49±0,17**</b>
<b>Habitual users</b>	<b>21,7±0,98</b>	<b>24,4±0,96</b>	<b>19,45±0,45*</b>	<b>4,37±0,24*</b>	<b>4,55±0,17*</b>

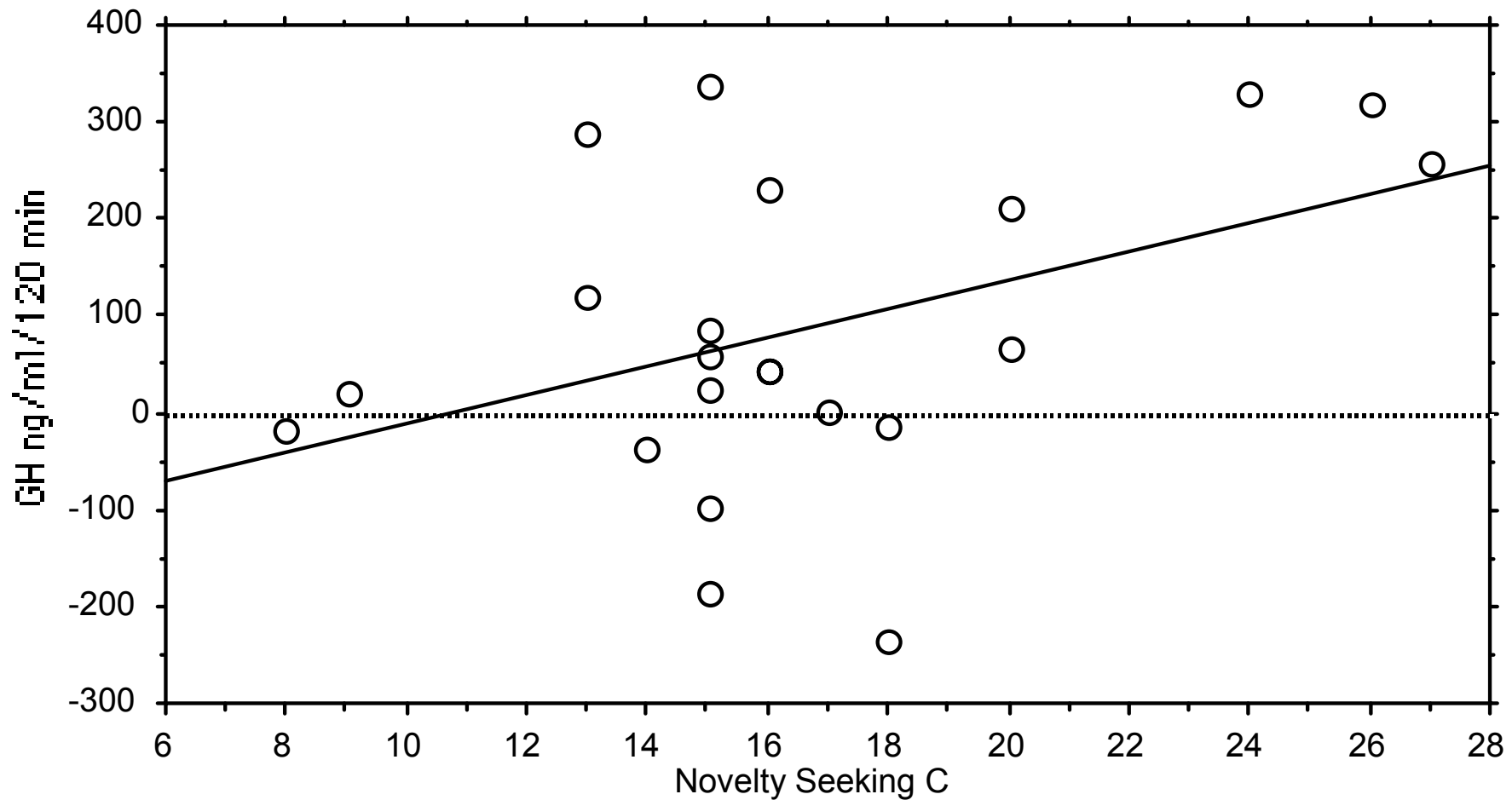
+ p&lt; 0.001

\*\* p&lt; 0.01

Psychoneuroendocrinology 25:479-496, 2000.

Neuroendocrine correlates of temperamental traits in humans.

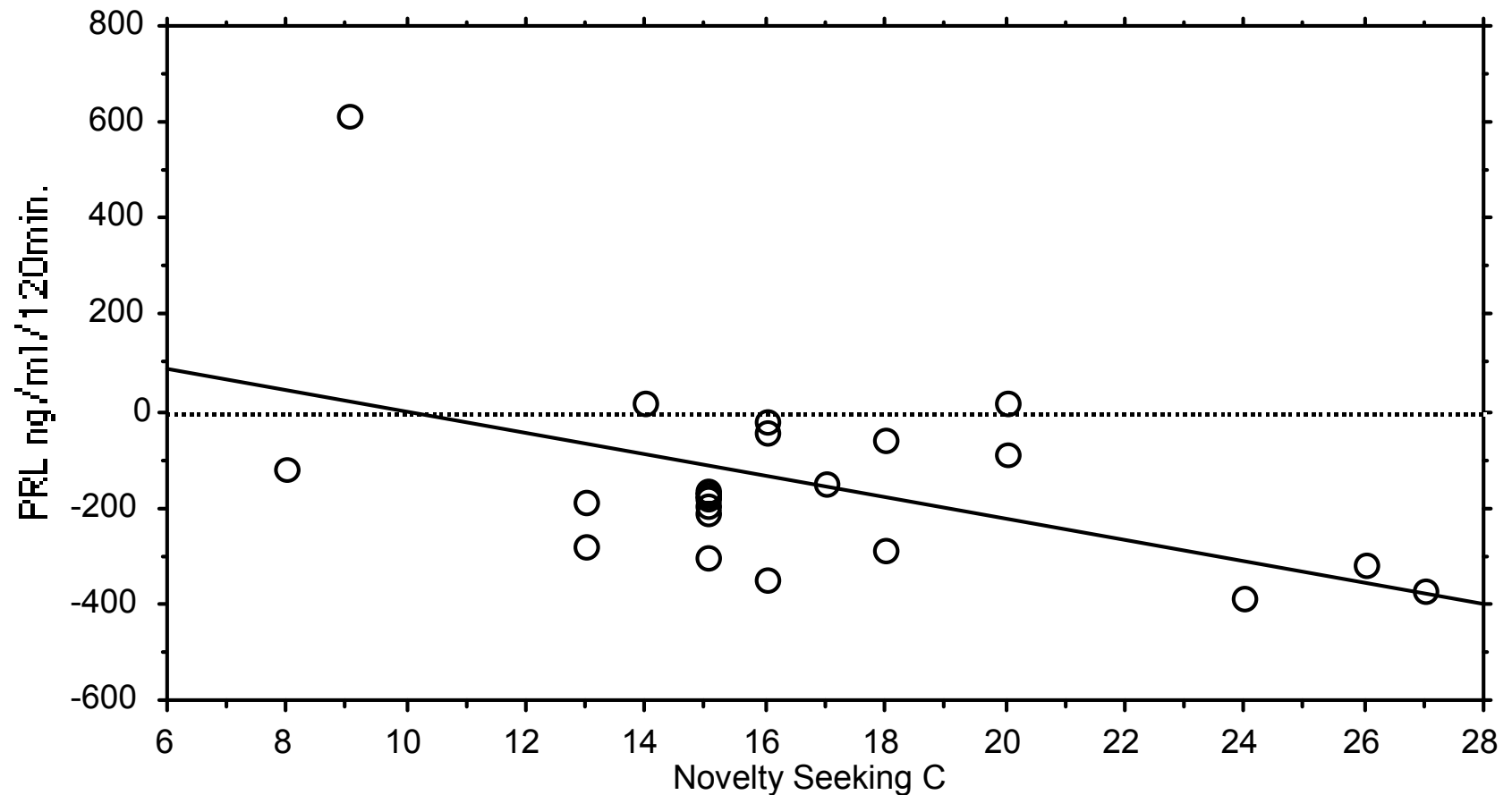
**Gerra et al.**



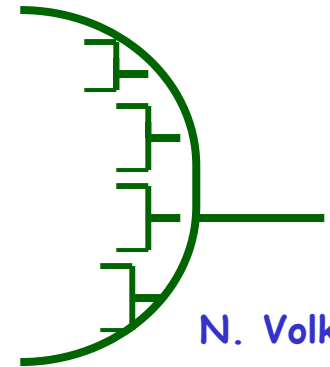
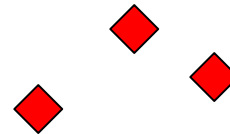
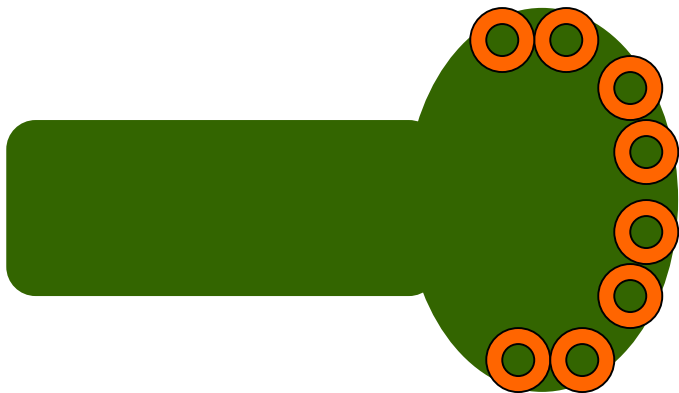
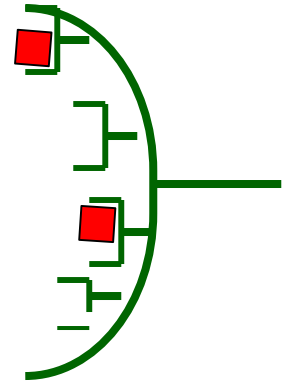
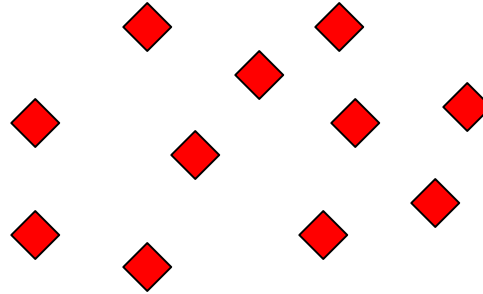
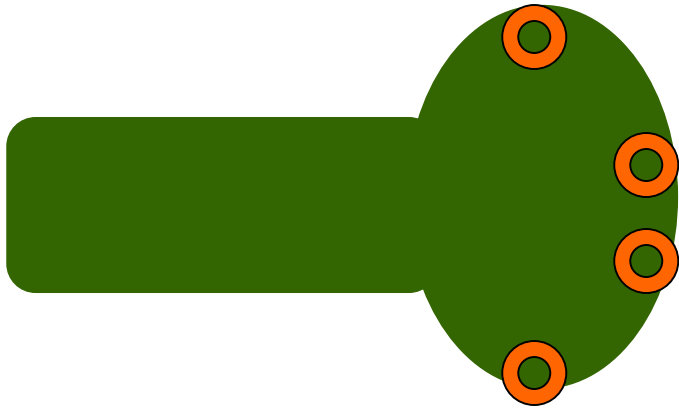
Psychoneuroendocrinology 25:479-496, 2000.

Neuroendocrine correlates of temperamental traits in humans.

**Gerra et al.**



# Attention deficit hyperactivity disorder and conduct disorder



reduction in extracellular DA  
reduction in rewarding signal

N. Volkow and  
J. Fowler, 2002

# CHILDREN and ADOLESCENTS



**USUALLY  
INTERESTING  
ACTIVITIES**

**PROVIDE FEWER  
REWARDS**

**UNDERFED  
REWARD CIRCUITS**



## Alcohol Clin Exp Res

P3 event-related potential, dopamine D2 receptor A1 allele, and sensation-seeking in adult children of alcoholics.

Ratsma et al., 2001

- P3 amplitude
- High sensation-seeking
- A1 allele

**COMMON RISK FOR ALCOHOLISM**



**The A1 allele of the D2 dopamine receptor gene is associated with high dopamine transporter density in detoxified alcoholics.**

**Laine et al., 2001**

**Alcoholics with the A1/A2 genotypes  
had statistically significantly higher DAT densities  
than subjects with the A2/A2 genotypes**

## Alcohol

**Stress as a mediating factor in the association between the DRD2 TaqI polymorphism and alcoholism.**

**Madrid et al., 2001**

**DRD2 genotype-phenotype associations  
depend  
on the magnitude of stress exposure**

**variability in DRD2 study outcomes may in part be explained  
by this gene-environment interaction**

**Dopamine D2 receptor gene (DRD2) is associated with alcoholism with conduct disorder.**

**Lu et al., 2001**

**DRD2 might be associated with conduct disorder  
or a predisposition to  
both conduct disorder and alcoholism**

# **Contribution of genetics to the concept of risk status for alcohol dependence**

**Gorwood, 2000**

- the gene coding for the dopamine 2 receptor may be more specifically involved in severe and comorbid alcohol-dependence
- the gene coding for the serotonin transporter may increase the suicidal risk in alcohol-dependent patient
- the quality of the withdrawal process is partly explained by the existence of a specific genotype of the dopamine transport gene

**The TaqI A1 allele of the dopamine D2 receptor gene and alcoholism in Brazil: association and interaction with stress and harm avoidance on severity prediction.**

**Bau et al., 2000**

**DRD2 TaqI A1 allele**

**significant interaction  
with**

- stress**
- harm avoidance**

**in predicting the severity of alcohol dependence**

# **Impulsiveness and discounting of delayed rewards**

central serotonergic dysfunction

a significant association between 5-HT<sub>2A</sub> A alleles and impulsive traits

impaired serotonin system: characteristic of adult alcoholics with impulsive behavior

# Il genotipo SS nei tossicodipendenti: alterazione del trasporto presinaptico della serotonina

Centro Studi Farmaco-tossicodipendenze - AUSL - Parma, 2001

RIS - Reparto Investigazioni Scientifiche Carabinieri di Parma, 2001

Table 1. The 5-HTTLPR genotype and allele frequencies.

	LL%	LS%	SS%	L%	S%
Heroin Dependent Subjects	26,0	44,4	29,6	48,1	51,9
Control subjects	37,7	50,8	11,5	63,1	36,9

Table 2. Genotype, suicide attempters and not attempted suicide among heroin dependent subjects.

	LL%	LS%	SS%	L%	N%
Suicide attempters	21,4	35,7	48,8	39,3	60,7
Non suicide attempters	27,5	47,5	25	51,3	48,7

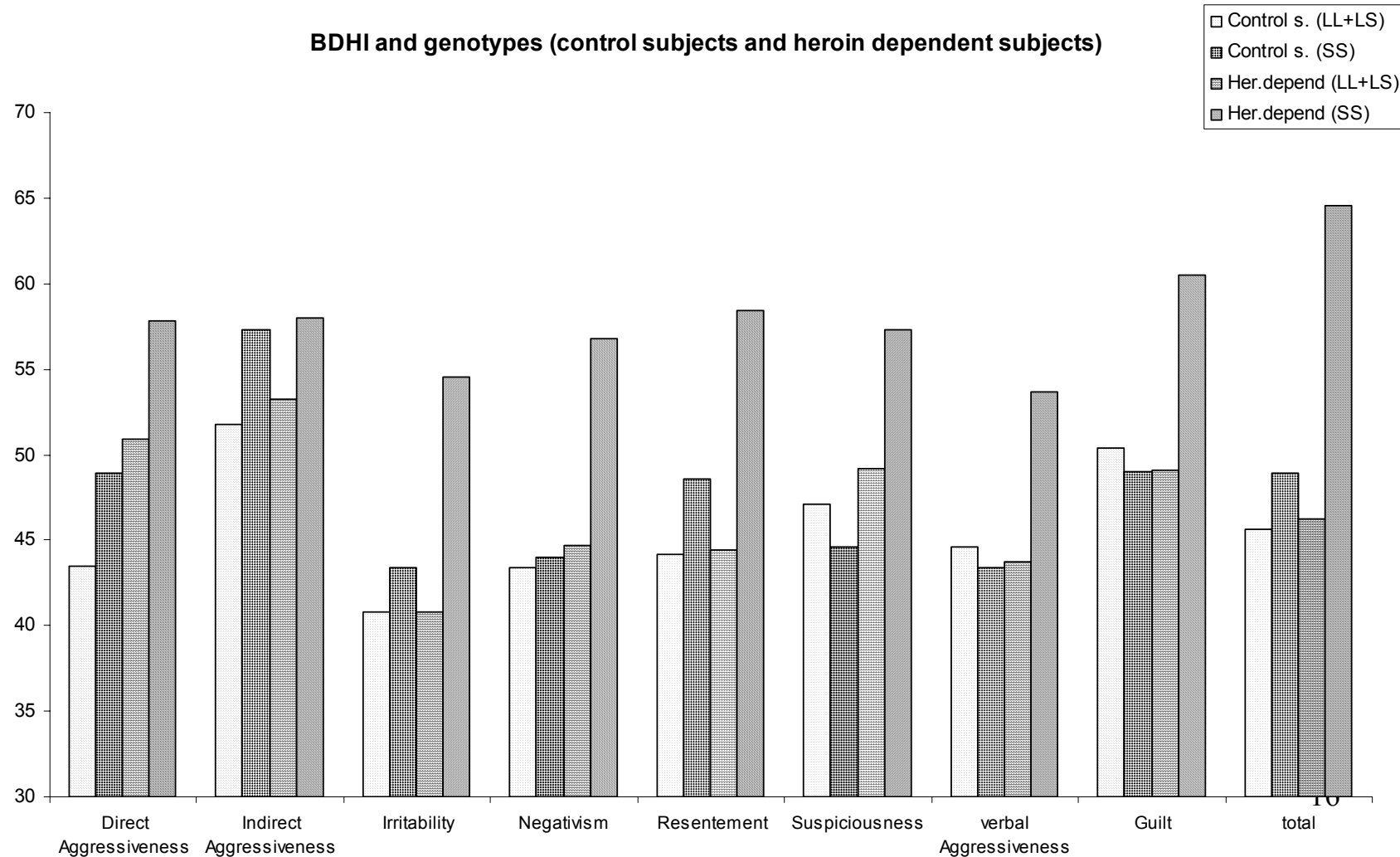
Table 3. Genotype, violent offenders and non violent offenders.

	LL%	LS%	SS%	L%	S%
Offenders	13,8	51,7	34,5	39,7	60,3
Non offenders	50,0	38,9	11,1	69,4	30,6

# Il genotipo SS nei tossicodipendenti: alterazione del trasporto presinaptico della serotonina

Centro Studi Farmaco-tossicodipendenze - AUSL - Parma, 2001

RIS - Reparto Investigazioni Scientifiche Carabinieri di Parma, 2001





**Association of a polymorphism of the serotonin 1B receptor gene and alcohol dependence with inactive aldehyde dehydrogenase-2.**

**Hasegawa et al., 2002**

genetic variability of the 5HT1B receptor is involved in the development of some type of alcohol dependence

Biol Psychiatry

**Association between suicide attempts and 5-HTTLPR-S-allele in alcohol-dependent and control subjects: further evidence from a German alcohol-dependent inpatient sample.**

**Preuss et al., 2001**

Am J Med Genet

**Association study of serotonin transporter gene regulatory region polymorphism and alcoholism.**

**Matsushita et al., 2001**

**The frequency of the homozygous short allele was significantly higher in alcoholic binge drinkers than in nonbinge drinking alcoholics**

Alcohol

## **Serotonin transporter gene polymorphisms in alcohol dependence.**

**Thompson et al., 2000**

**a trend toward increased frequency of the S promoter allele in:**

- alcohol-dependent,**
- alcoholic-Tourette syndrome**
- Tourette syndrome patients**

Am J Med Genet

## **Association of 5HT2A receptor gene polymorphism and alcohol abuse with behavior problems.**

**Hwu and Chen, 2000**

**alcoholism is heterogeneous and male alcohol abuse with behavioral problems was found associated with T/C 102 polymorphism of the 5HT2A receptor gene**

**Serotonergic function in cocaine addicts: prolactin responses to sequential D,L-fenfluramine challenges.**

**Buydens-Branchey et al., 1999**

**Paternal history of cocaine addicts:**

**Type 1**

- no history of paternal alcoholism
- non-aggressive behavior
- normal response to d-fenfluramine

**Type 2**

- paternal history of alcoholism
- aggressive behavior
- blunted responses to d-fenfluramine

# **Substance use disorders and antisocial personality disorder**

higher outward-directed aggressiveness in addicted individuals

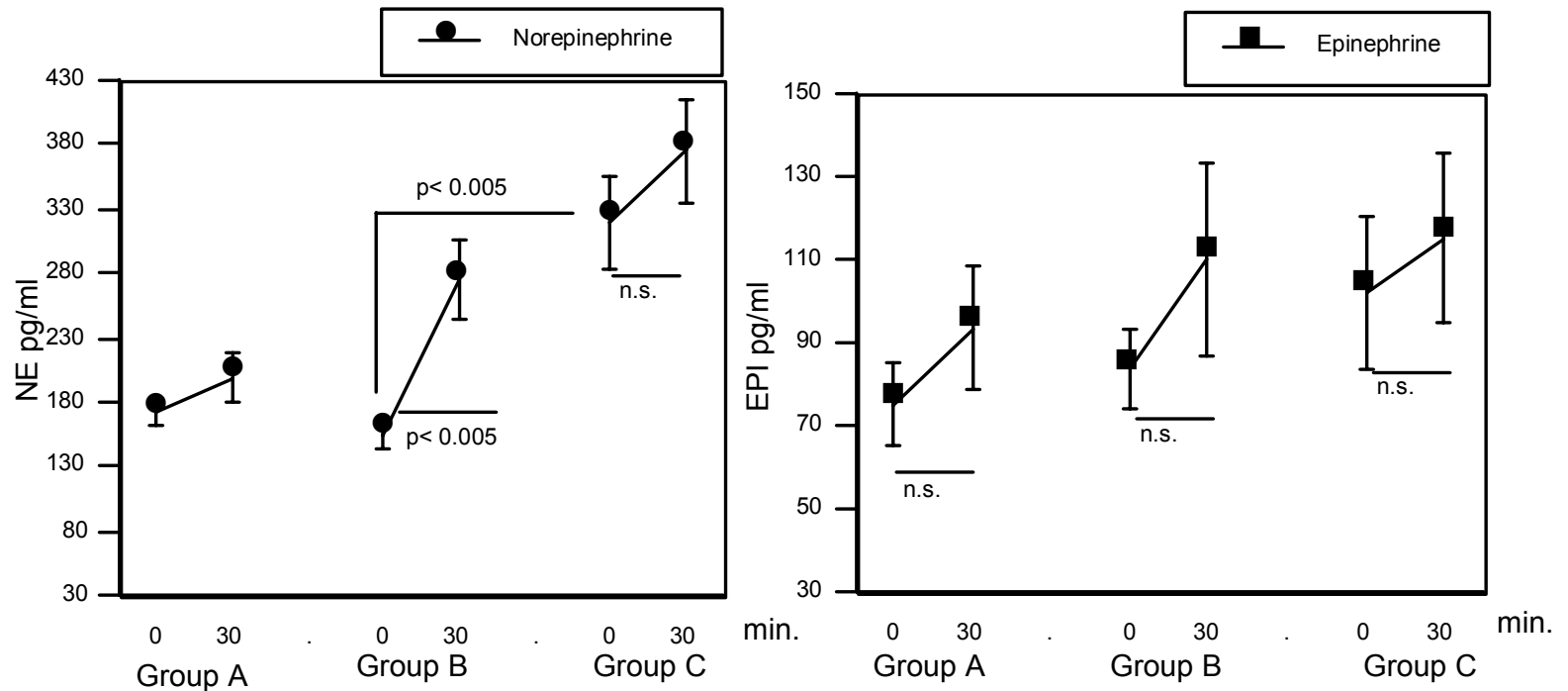
correlation of levels of aggressiveness with norepinephrine values

methadone patients

ecstasy users

# Neurotransmitter-hormonal responses to psychological stress in peripubertal subjects: relationship to aggressive behavior.

Gerra et al., Life Sciences 62(7),617-625 1998.



Psychiatry Res

**Association of a regulatory polymorphism in the promoter region of the monoamine oxidase A gene with antisocial alcoholism.**

**Samochowiec et al., 1999**

**low-activity 3-repeat allele of the MAOA promoter polymorphism:**

**increased susceptibility to antisocial behavior rather than alcohol dependence per se**

Genomics 1999 Feb 1;55(3):290-5

**Sequence analysis of exon 8 of MAO-A gene in alcoholics with antisocial personality and normal controls.**

**Parsian**

**mutations in the MAO-A gene may play a role in the development of alcoholism associated with ASP**



# Noradrenalina

**Mutazioni del gene che codifica per la noradrenalina**

**mutazione del gene che codifica per l'enzima MAO: si associa all'alcolismo di tipo deviante e antisociale**

**(Parsian, 1999)**

**mutazione del gene che codifica per l'enzima COMPT: si associa a più elevati livelli di intake di alcool o alla vulnerabilità per l'alcolismo a esordio tardivo**

**(Kauhanen et al., 2000)**

**mutazione del gene che codifica per l'enzima tirosina-idrossilasi (si associa a più intensi sintomi astinenziali)**

**(Sander, 1998)**

# Rischio per l'alcolismo e il Gaba

**Figli di alcolisti con variazioni genetiche:**

**problematiche dell'umore e dell'ansia**

- **mutazioni del gene che codifica per il transporter di una subunità del Gaba**

(Schuckit et al., 1999)

## **Rischio per l'alcoolismo e recettori oppioidi**

**Alterazione del gene che codifica per i recettori  $\mu$  (altera la sensibilità dopaminergica)**

(Town et al., 1999)

## **Rischio per l'alcoolismo e meccanismi metabolici**

**Polimorfismo genetico: alterazioni meccanismi metabolici che sono connessi alla trasformazione dell'alcool in acetaldeide e acido acetico**

(Chrostek e Szmitkowski, 1998)

# **Association between mu opioid receptor gene polymorphisms and Chinese heroin addicts.**

Szeto et al., 2001, Neuroreport

**Mu opioid receptor (MOR) has been shown to be associated with alcoholism and opioid dependence**

**This study suggests that the variant G allele of both A118G and C1031G polymorphisms may contribute to the vulnerability to heroin dependence.**

# Single-nucleotide polymorphism in the human mu opioid receptor gene alters beta-endorphin binding and activity: possible implications for opiate addiction.

Bond et al., 1998, Proc Natl Acad Sci

single-nucleotide polymorphism in the mu opioid receptor gene can alter binding and signal transduction in the resulting receptor

implications for

normal physiology,

therapeutics,

vulnerability to develop or protection from diverse diseases including the addictive diseases.



# **Fattori di rischio per i disordini da uso di sostanze psicoattive**

**Merikangas et al., 1998**

- **socio-relazionali**
- **genetico-biologici**
- **culturali**
- **ambientali**

# **Studi gemellari rispetto al manifestarsi dell'alcolismo**

**concordanza elevata tra omozigoti, rispetto agli eterozigoti**

(Enoch e Goldman, 1999)

**elevato indice di ereditarietà dell'alcolismo pari a 0,42-0,75**

**esordio precoce: indice=0,73**

**esordio tardivo: indice=0,30**

(Gelernter et al., 1993)

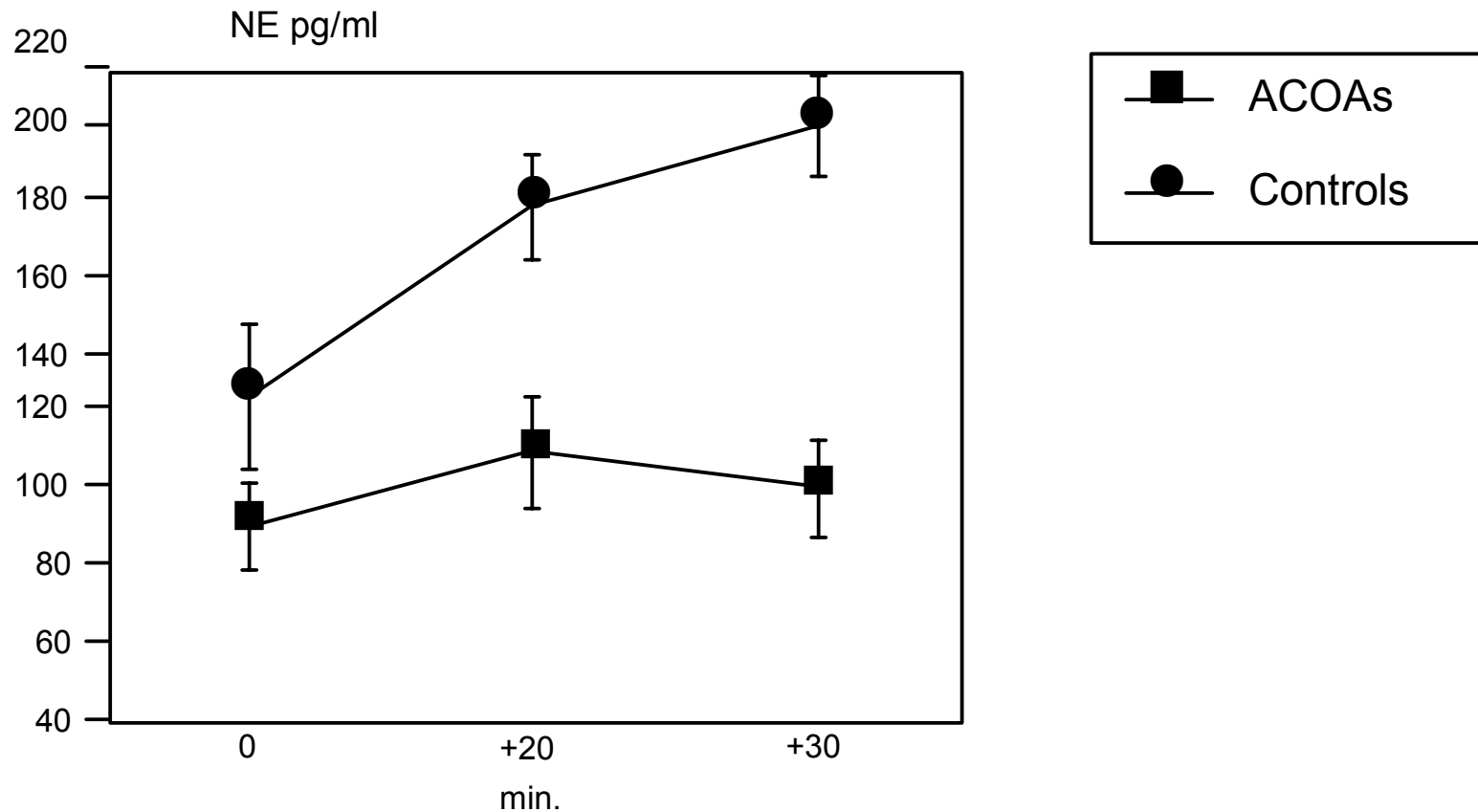
**predisposizione alla dipendenza estesa a più sostanze tra i parenti di primo grado degli alcoolisti**

(True et al., 1999)



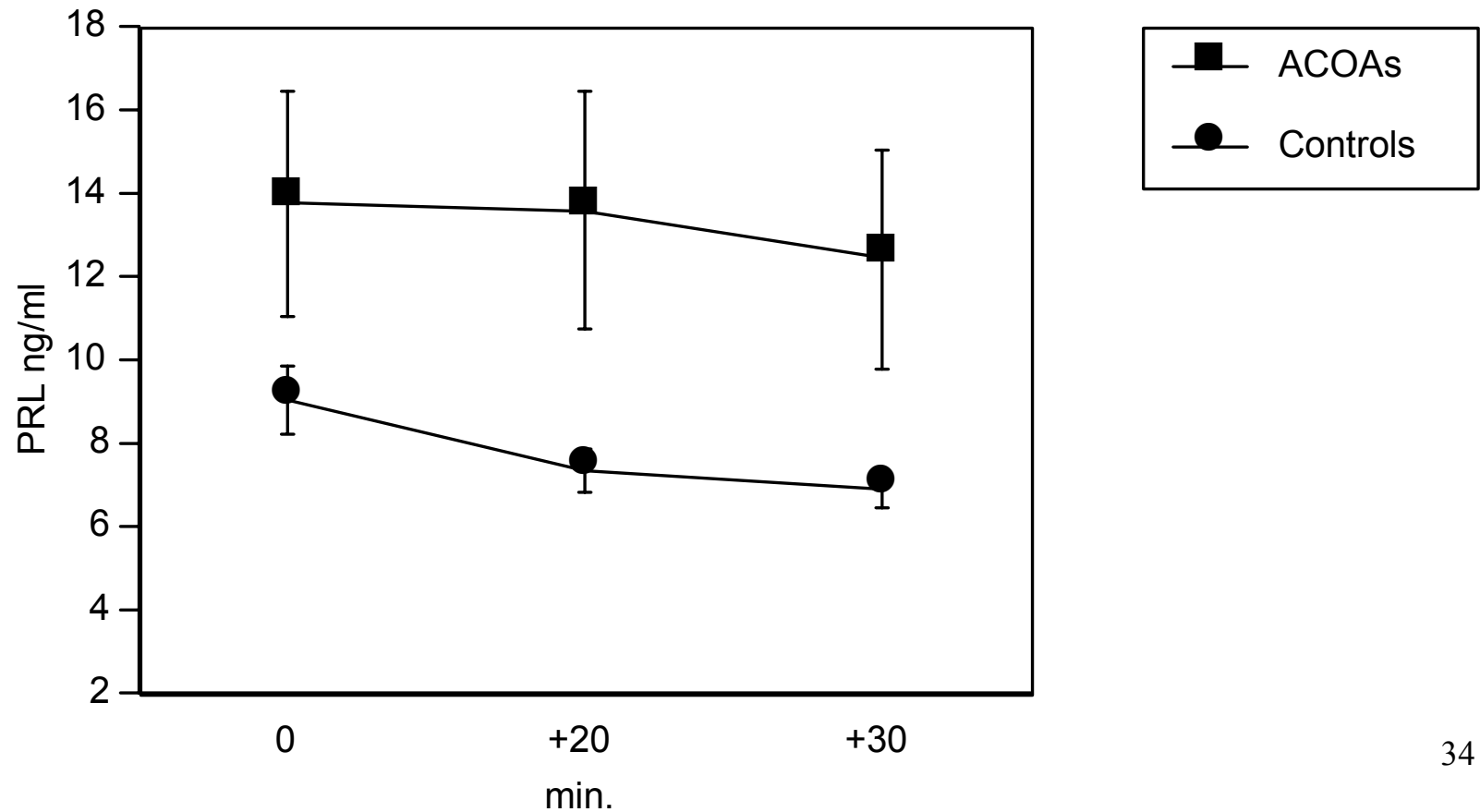
**Experimentally induced Aggressiveness in adult children of alcoholics (ACOAs): preliminary behavioral and neuroendocrine findings.**

Gerra et al., 1999



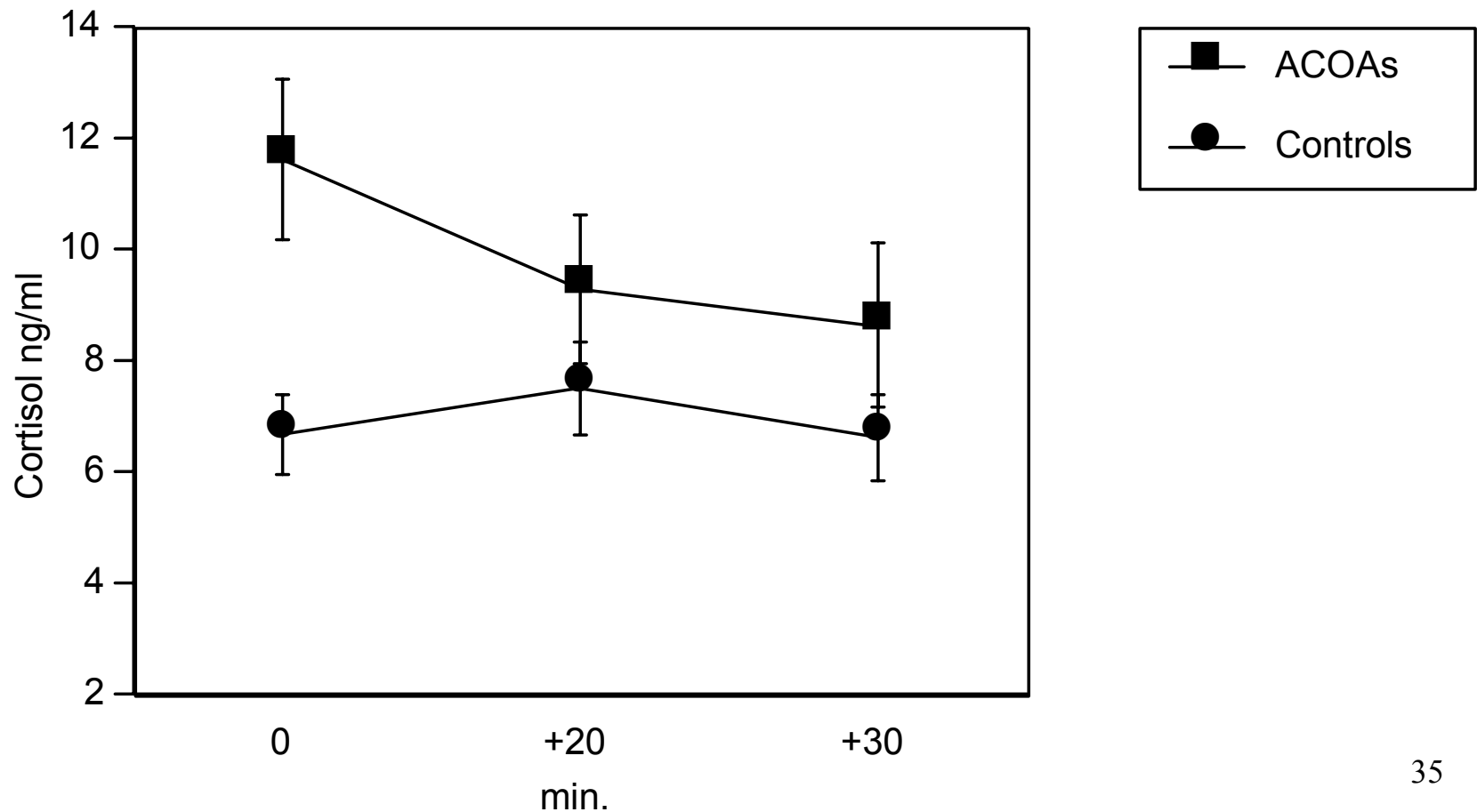
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**Experimentally induced Aggressiveness in adult children of alcoholics (ACOAs): preliminary behavioral and neuroendocrine findings.**

Gerra et al., 1999

**Gained money**

**Subtracted money**

ACOAs	CONTROLS	F	p
19.977.7±1.824.6	28.742.9 ±2.213.6	4.6	<.05
1.688.8 ±563.3	12.653.6±2.017.2	9.2	<.005

**Experimentally induced Aggressiveness in adult children of alcoholics (ACOAs): preliminary behavioral and neuroendocrine findings.**

Gerra et al., 1999

**Psychometric measures in ACOAs and control subjects, means ( $\pm$ SDs)**

Variables	ACOA s	Controls	F	p
BDHI guilt	64.8 $\pm$ 3.3	49.2 $\pm$ 1.6	15.7	<001
BDHI resentment	57.8 $\pm$ 1.9	49.2 $\pm$ 1.9	6.4	<05
BDHI direct	43 $\pm$ 1.6	47.4 $\pm$ 1.3	ns	ns
BDHI total	62 $\pm$ 2.7	53.64 $\pm$ 2.1	ns	ns
Aggressiveness VAS	2.2 $\pm$ 1.4	6.9 $\pm$ 1.9	3.8	<05
MMPI- hysteria	71.4 $\pm$ 6.1	56.6 $\pm$ 8.4	10.8	<005
MMPI- hypochondria	71 $\pm$ 4.2	54 $\pm$ 1.5	20.1	<001
MMPI-paranoia	58.5 $\pm$ 4.9	47.9 $\pm$ 1.7	4.7	<05
TPQ: reward dependence	19.4 $\pm$ 168	13.6 $\pm$ .39	10.9	<005

# **LA GRAVIDANZA: CONDIZIONE AMBIENTALE CHE INFLUENZA LA BIOLOGIA DEL CERVELLO DELLA PROLE**

**NELL'ANIMALE  
DA ESPERIMENTO**

**STRESS DA IMMOBILIZZAZIONE**



**alterate noradrenalina e dopamina nella prole**

**STRESS DA SOVRAFFOLLAMENTO**



**alterati CRF ACTH e cortisolo nella prole**

**CONSEQUENTI**

**alterazioni del comportamento sessuale e dell'aggressività nell'animale divenuto adulto**

**(Reznikov, et al., 1999; Faraone and Biederman, Biol Psychiatry 1998 )**

The neurobiology of stress in human pregnancy: implication for the development of the fetal nervous system.

Wadhwa et al.

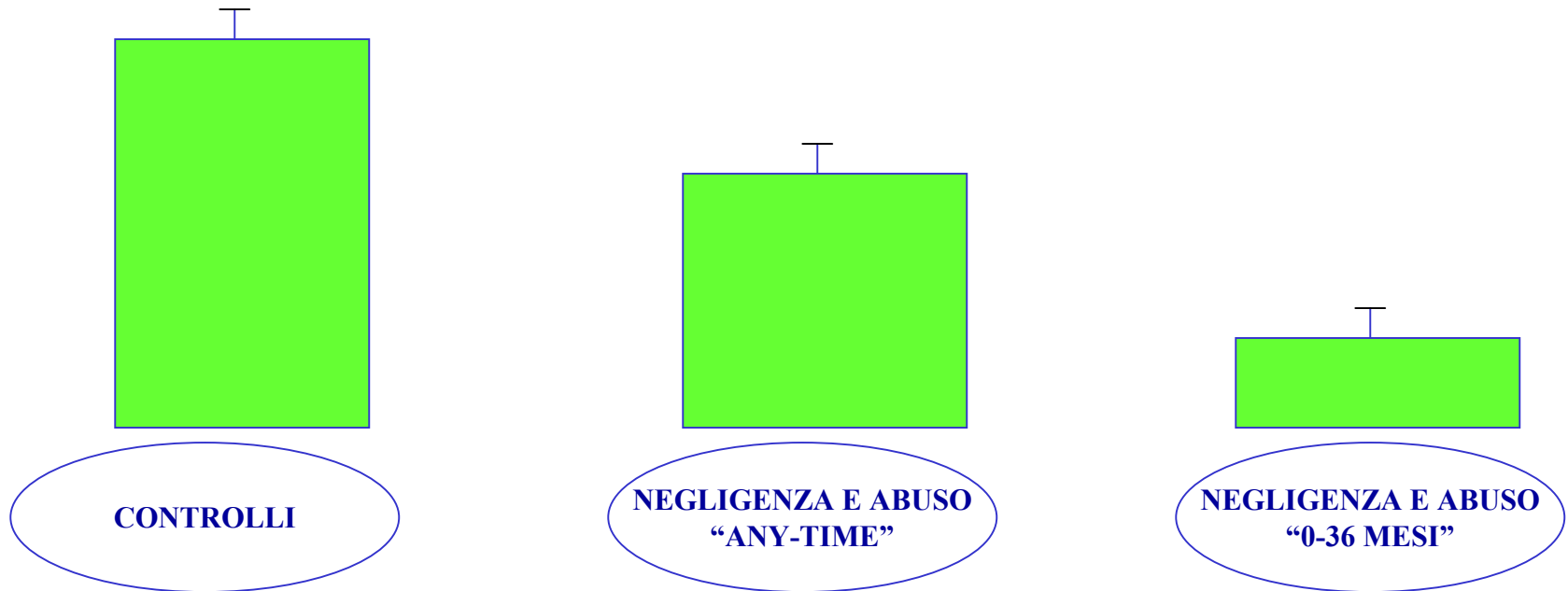
Le influenze dello stress prenatale attraverso l'azione degli ormoni della madre sullo sviluppo del feto possono persistere dopo la nascita



# Serum dopamine beta hydroxylase and maltreatment in psychiatrically hospitalized boys

Galvin et al., 1991, 1995, 1997

LA DOPAMINA BETA-IDROSSILASI  
ENZIMA CHIAVE NEGLI EQUILIBRI DELLE MONOAMINE CEREBRALI E'  
RIDOTTA NEGLI ADOLESCENTI CON DISTURBO DELLA CONDOTTA



GLI ELEMENTI AMBIENTALI E RELAZIONALI INCIDONO  
SULLA BIOLOGIA DEL CERVELLO



**Polimorfismi genetici**

**Stress gravidanza**

**Alterazioni  
temperamento  
del bambino**

**Attaccamento parentale insicuro e disorganizzato  
Difficoltà interazione madre bambino**

**Alterazioni della cascata della gratificazione  
(alterazioni monoamine e peptidi cerebrali)**

**Rischio di disturbi da uso di  
sostanze**