An Integrated Biopsychosocial Causal Model of Suicidal Behavior

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Disclosures: 1. This talk is based on research funded by NIMH. 2. PI on two recent PET study grants unrelated to the topic of this talk funded by Novartis and GSK.

Suicidal Behavior

- Is not a normal response to stress.
- It is a complication of psychiatric illness and psychosocial crisis in a vulnerable person.

Clinical Identification of Higher Risk Populations as the First Predictor

- Past suicide attempt.
- Family history of a suicide attempts.
- Current or past ideation with a plan. Most severe ideation lifetime predicts risk for suicide.
- All indicate presence of diathesis or vulnerability to react to stress with suicidal behavior.

The Second Predictor?

- Biology with genetic testing or brain scan.
- Cognitive Testing of decision-making.

We seek biological traits that are transmitted in families with suicidal behavior

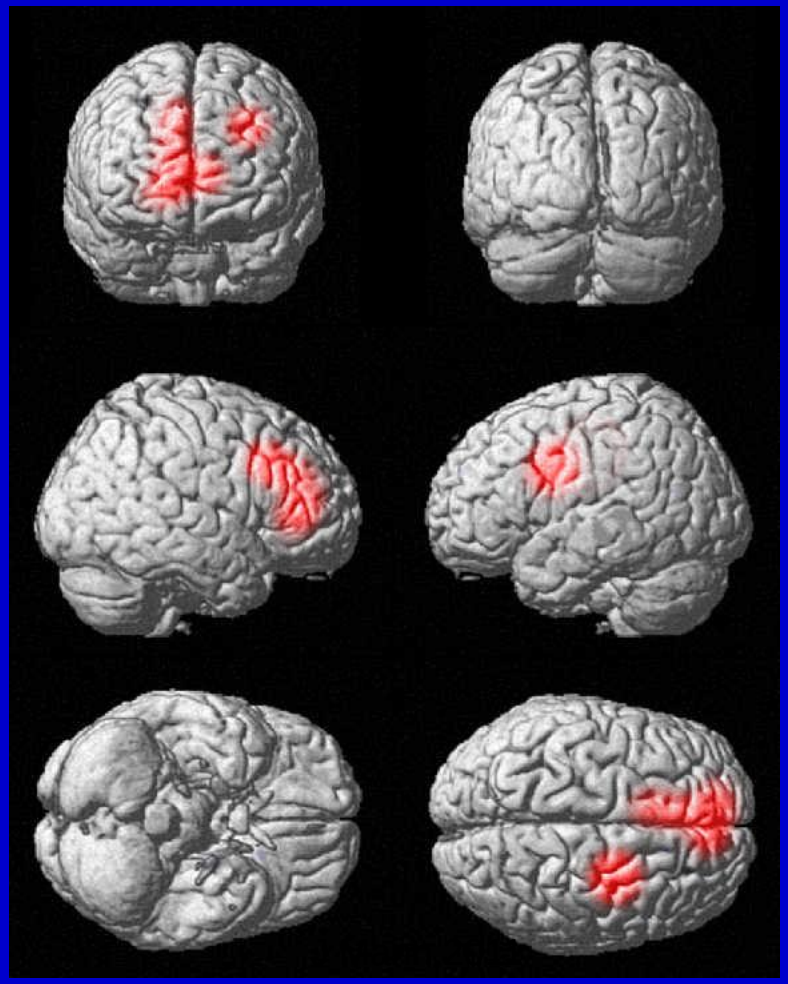
- Early life experience and genes and their interaction have formative effects on the brain.
- Enduring behavioral traits are due to enduring biological characteristics.
- Clinical and biologic traits can predict future behavior.

Probability and Intent for Suicidal Behavior

Impulsivity related to probability of an attempt.

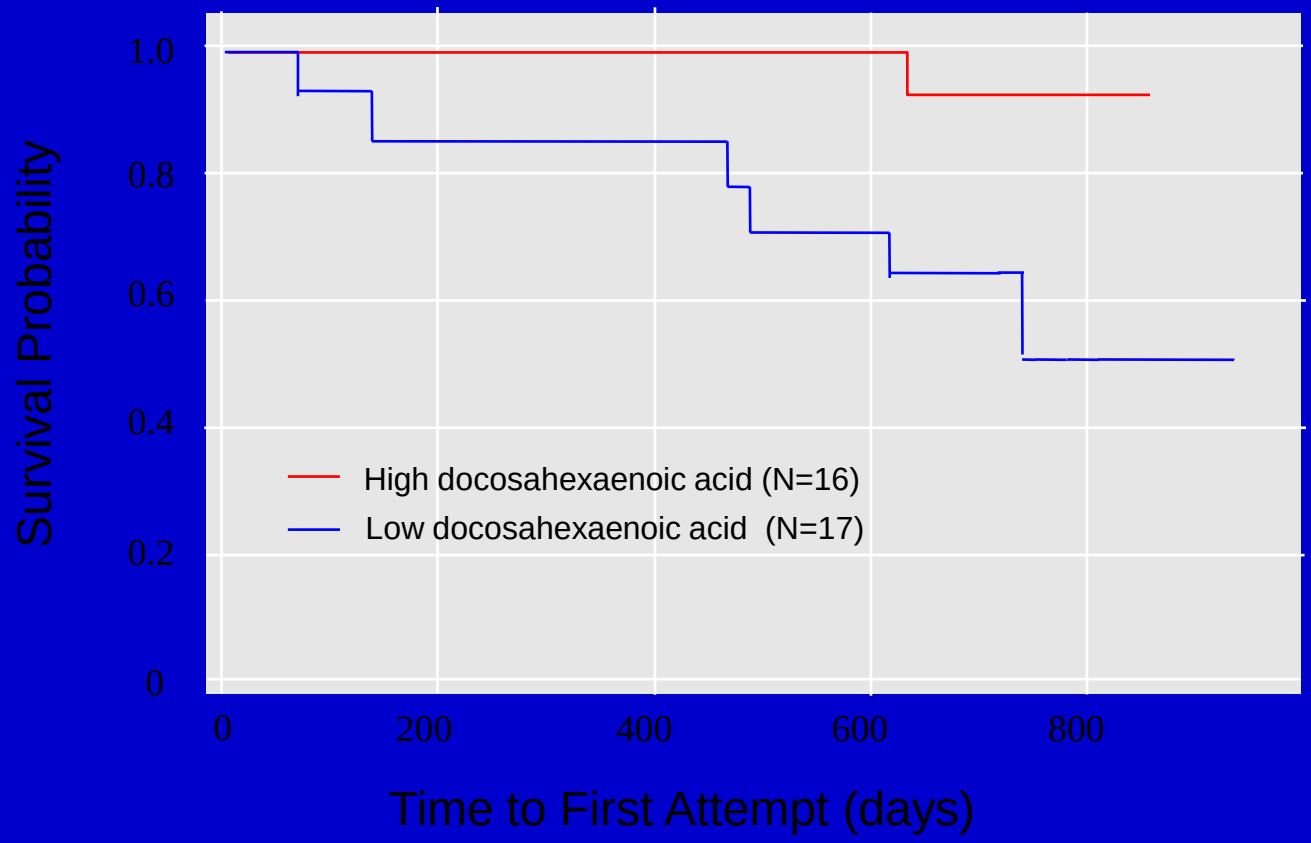
- Hopelessness, impaired problem-solving or cognitive rigidity or pessimism related to probability.
- Suicidal intent related to lethality of attempt.

Brain Activity on PET FDG after Serotonin Release Related to Suicide Attempt Behavior



Size of abnormality is related to impulsivity and suicide intent thereby influencing lethality (Oquendo et al AJP

The Role Of Diet: a gene environment interaction



Kaplan Meier Survival Plot of Suicide Attempt Outcome by DHA Status (Median split into low and high levels).

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Sublette, et al. Am J Psychiatry 2006

CSF 5-HIAA: an index of brain serotonin system trait activity

- The odds of suicide are estimated to be four and a half times greater for the low CSF 5-HIAA group compared with the high CSF 5-HIAA group.
- Low CSF 5-HIAA reflects less serotonin release based on low serotonin/5-HIAA levels in suicides' brainstem.
- Enhancing serotonin transmission may have a protective effect against the risk due to low serotonin transmission.

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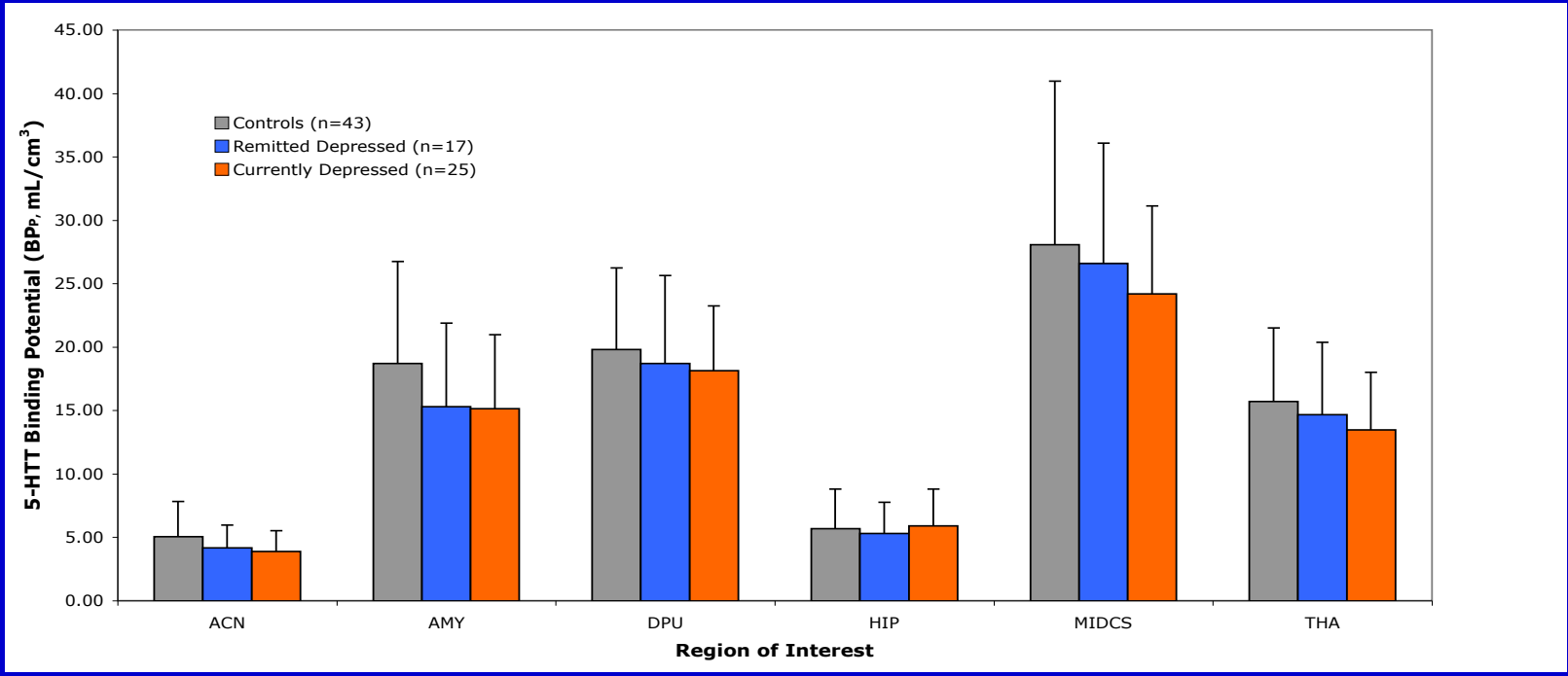
Serotonin transporter binding low in remitted Major Depressive Disorder



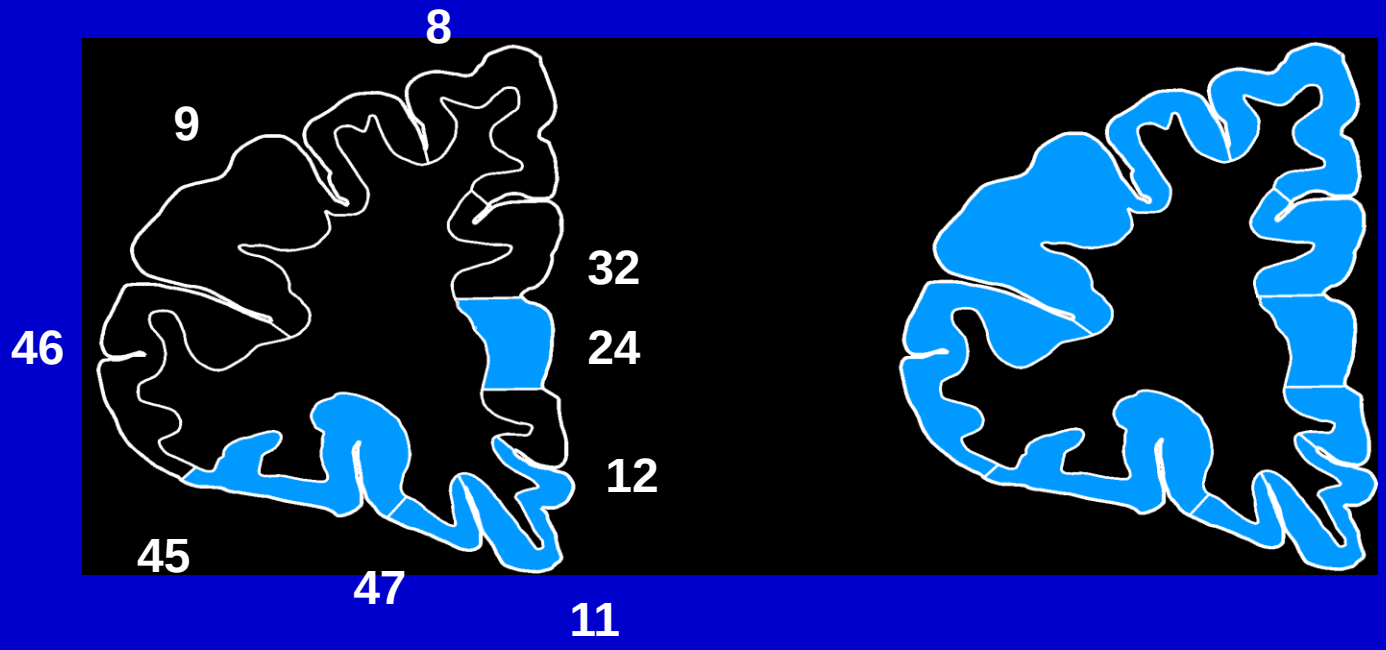
Evidence of a serotonin system trait abnormality

Prediction of Suicide in Major Depression from Brain Serotonin Circuitry

- Suicides have low serotonin transporter binding in anterior cingulate and ventral prefrontal cortex.
- Low transporter binding on PET in amygdala and trend in ventral prefrontal cortex (Miller et al) are associated with suicide attempts.
- Therefore there is a biologic phenotype associated with suicide that can be detected in living patients before suicide.

Postmortem Serotonin Transporter Binding in Suicide and Depression

Suicide (n=45) **Major Depression (n=33)**



Decreases

Arango et al., *Progress Brain Res., 2002*

Functional 5-HTTLPR Promotor Polymorphism

- Meta-analyses suggested it is associated with mood disorders and perhaps suicide attempts. But not very strong finding.

Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, McClay J, Mill J, Martin J, Braithwaite A, Poulton R. Science, 2003. A functional polymorphism in the promoter region of the serotonin transporter (5-HT T) gene was found to moderate the influence of stressful life events on depression. Individuals with one or two copies of the short allele of the 5-HT T promoter polymorphism exhibited more depressive symptoms, diagnosable depression, and suicidality in relation to stressful life events than individuals homozygous for the long allele. This epidemiological study thus provides evidence of a gene-by-environment interaction, in which an individual's response to environmental insults is moderated by his or her genetic makeup.

No mother in early childhood means lower serotonin function in adulthood in monkeys with low expressing serotonin transporter gene allele: G*E effect that may explain aggressive traits, suicidal behavior or recurrent major depression.

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Childhood Adversity and Lower Serotonin Transporter Binding in Brain on PET in MDD

- 23 subjects with MDD and 10 reported childhood physical or sexual abuse.
- Underwent PET 11-C-McN5652 scans of transporter while medication free and in an major depressive episode.
- **Lower specific binding found in all brain regions (p = .014). No difference in nonspecific binding.**
- Independent of severity of depression and too few subjects to detect gene association.

5-HTTLPR May Affect Downstream Neural Circuitry via Serotonin Effects on Amygdala Responses to Adversity

Serotonin Transporter Genetic Variation and the Response of the Human Amygdala

Ahmad R. Hariri,[1] Venkata S. Mattay,[1] Alessandro Tessitore,[1] Bhaskar Kolachana,[1] Francesco Fera,[1] David Goldman,[2] Michael F. Egan,[1] Daniel R. Weinberger[1]*

Life Events or Stress and Suicide

- Life events are more common in patients with mood disorders compared to healthy controls.
- Suicide attempters are more hopeless and perceive fewer reasons for living given an equivalent number of life events compared with psychiatric controls.
- Life events may trigger a suicide attempt in vulnerable individuals. Serotonin transporter gene variant modulates the susceptibility to life events and is one example of a gene-environment interaction.

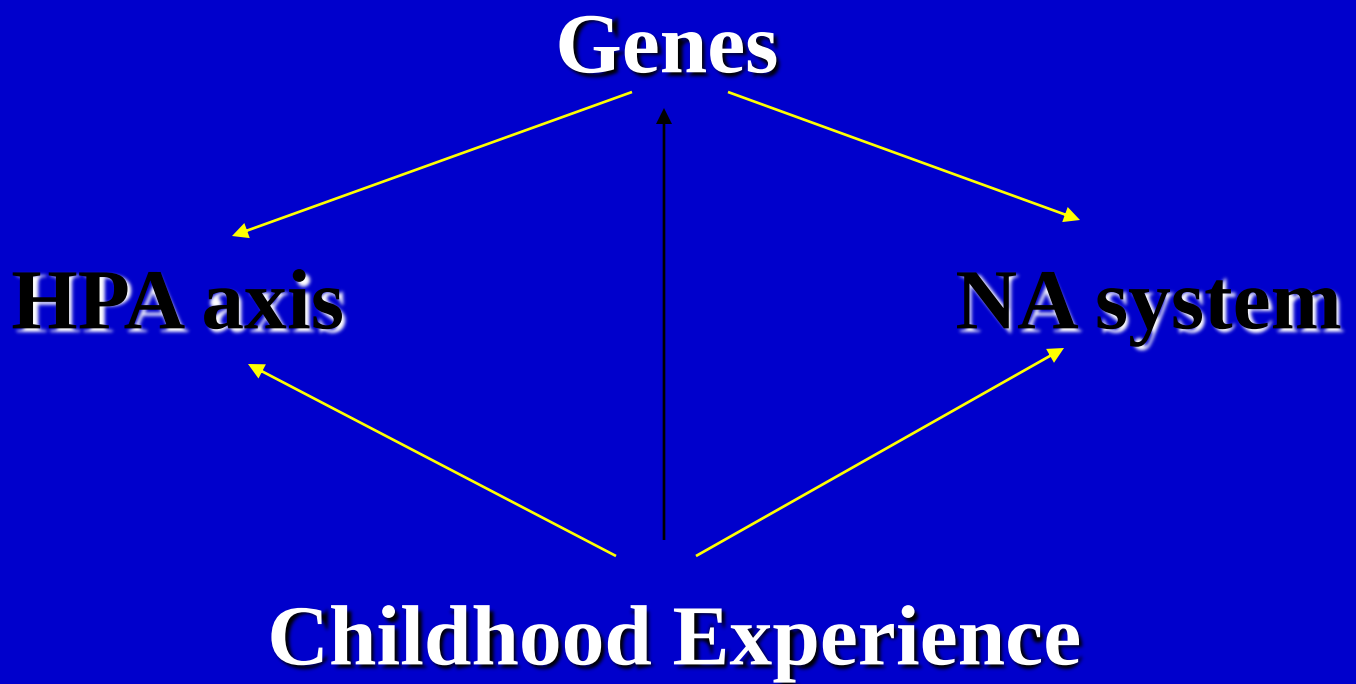
Connectivity

- Pezawas et al 2005 found decreased functional coupling between amygdala and ACC in S allele carriers and Anand et al 2009 reported the same finding in mood disorders.
- Heinz et al 2005 reported less functional coupling in S allele carriers between amygdala and perigenual ACC but more coupling with medial PFC.
- Pacheco et al 2009 reported white matter (DTI) left uncinate fasciculus abnormalities in S of L_G carriers. Wang et al 2009 link this to functional uncoupling between amygdala and ACC.

How does 5-HTTLPR affect risk for adult depression and suicidal behavior?

- Most postmortem binding studies and *in vivo* imaging studies do not find low serotonin transporter binding in the subjects with the low expressing allele.
- We hypothesize that this gene variant has a downstream developmental effect that accounts for lower serotonin after maternal deprivation, amygdala hyper-reactivity and depression.
- Ansorge et al found SSRI shortly after birth in rodents produced an adult depressive phenotype like that seen in HTT gene KO. Yet SSRI helps depression in adults. Hence hypothesized a critical period in development where low HTT expression results in brain changes leading to stress sensitivity and risk of adult depression.

Stress Response Systems and Genes



Hypothalamic Pituitary Adrenal Axis Stress Response System

The odds of suicide completion are estimated to be four and a half times greater among dexamethasone non-suppressors compared with suppressors.

Childhood abuse in humans or maternal deprivation in rodents results in excessive cortisol and ACTH release after a laboratory stressor. This is part of a pattern of stress systems including the noradrenergic system being sensitized by childhood adversity (Heim and Nemeroff, 2001).

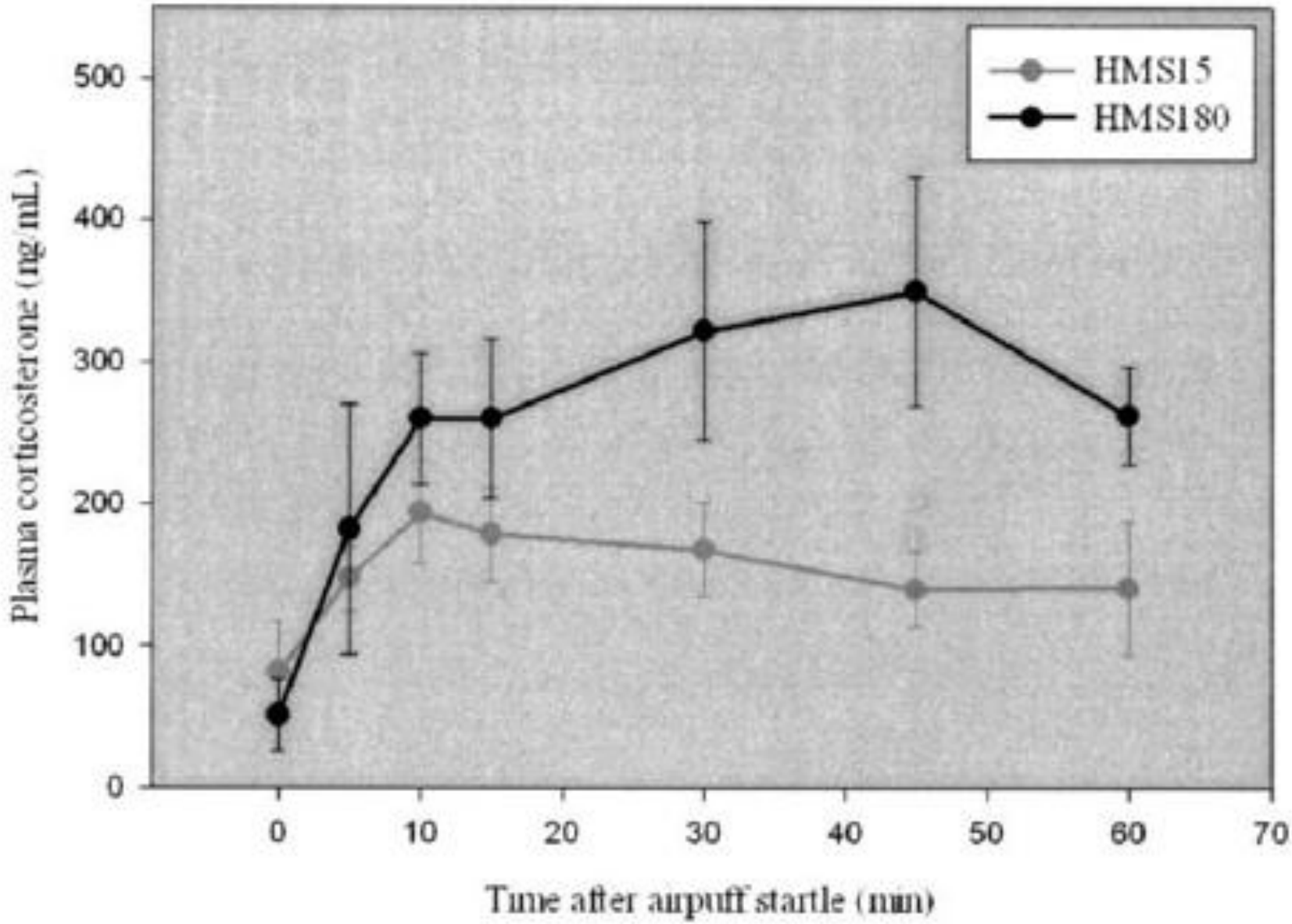


Figure 2. Plasma corticosterone concentrations (mean ± SEM) before and following APS in HMS15 ($n = 6$) and HMS180 ($n = 6$). APS, airpuff startle;

Long-Term Adaptations in Glucocorticoid Receptor and Mineralocorticoid Receptor mRNA and Negative Feedback on the Hypothalamo-Pituitary-Adrenal Axis Following Neonatal Maternal Separation

Charlotte O. Ladd, Rebecca L. Huot, K.V. Thrivikraman, Charles B. Nemeroff, and Paul M. Plotsky

Background: *Maternally separated rats exhibit exaggerated hypothalamic-pituitary-adrenal responses to an acute stressor but normal diurnal trough functioning. We hypothesized that maternally separated rats experience adequate proactive glucocorticoid negative feedback but deficient "reactive" negative feedback, contributing to prolonged hypothalamic-pituitary-adrenal stress responses.*

Methods: *We measured plasma adrenocorticotropic hormone and corticosterone concentrations following an acute stressor or 6 to 8 hours after dexamethasone administration in adult rats previously exposed to daily handling-maternal separation for 15 minutes (HMS15) or 180 minutes (HMS180) during postnatal days 2 to 14. We also examined regional mineralocorticoid receptor and glucocorticoid receptor messenger RNA density in these two groups.*

Results: *HMS180 rats appeared to escape dexamethasone suppression of plasma adrenocorticotropic hormone and corticosterone faster than their HMS15 counterparts ($p < .01$). In situ hybridization analysis revealed increased hippocampal mineralocorticoid receptor messenger RNA density ($p < .05$) with decreased cortical ($p < .05$) and hippocampal ($p < .05$) glucocorticoid receptor messenger RNA density in HMS180 versus HMS15 animals.*

Conclusions: *These results are consistent with the hypothesis that in rats exposed to moderate neonatal handling-maternal separation, enhanced proactive feedback maintains the hypothalamic-pituitary-adrenal axis during the diurnal trough, while decreased reactive feedback contributes to prolonged responsiveness of the hypothalamic-pituitary-adrenal axis following an acute stressor.*

Lower GR and greater MR expression

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Low hippocampal GCR expression and higher promotor methylation found in abused suicides

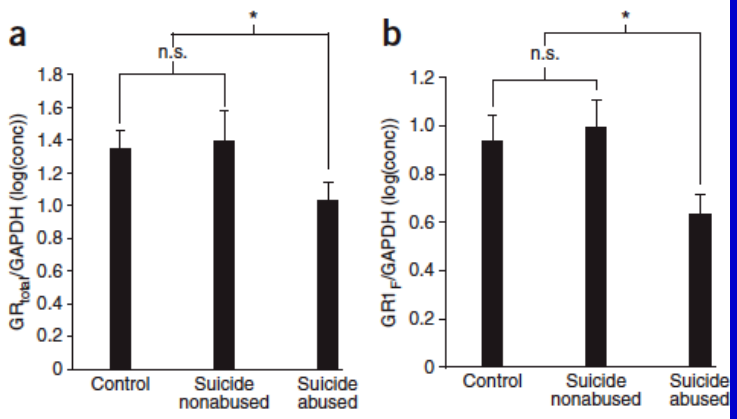

Figure 1 Hippocampal glucocorticoid receptor expression. (**a**,**b**) Mean ± s.e.m. expression levels of total glucocorticoid receptor (GR) mRNA (**a**) and

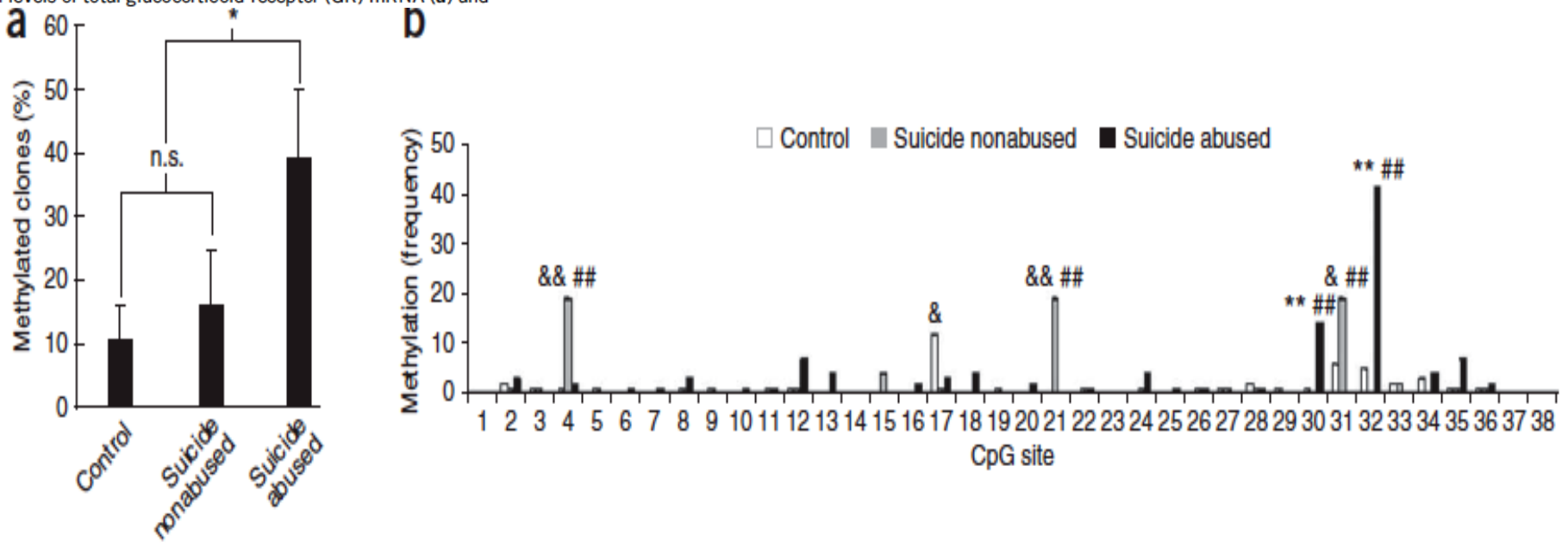

Figure 2 Methylation of the *NR3C1* promoter in the hippocampus. Twenty clones were sequenced for each subject for methylation mapping. (**a**) Mean ± s.e.m. percentage of methylated clones for suicide victims with a history of childhood abuse ($n = 12$), suicide victims without a history of childhood abuse ($n = 12$) and controls ($n = 12$). The methylation percentage was calculated as the number of clones with at least one methylated CpG site divided by the total

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McGowen et al., 2009. Nat Neurosci

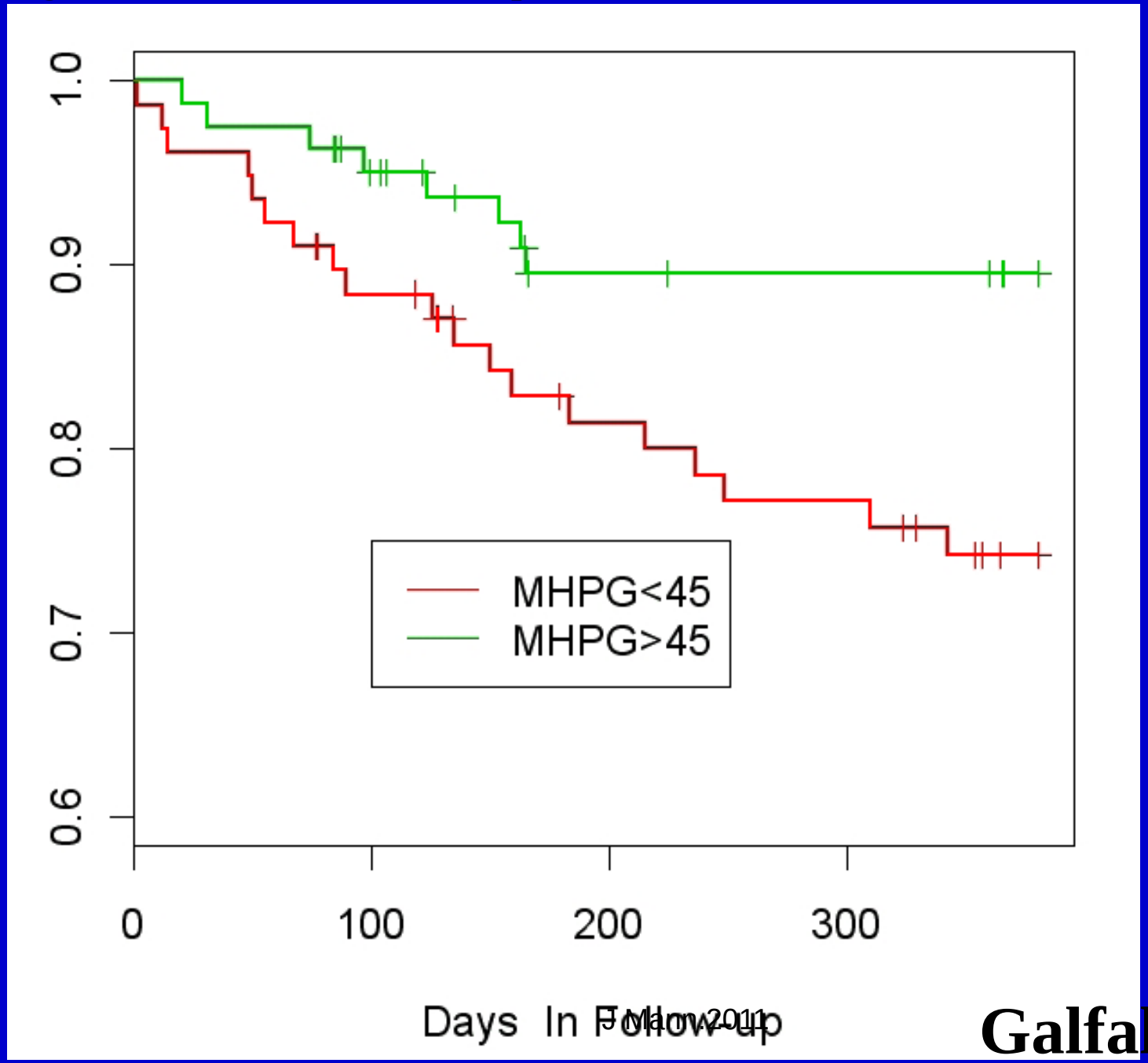
CSF MHPG: a state-trait index of noradrenergic function

We find heritability of CSF MHPG in baboons and others report alterations due to childhood adversity suggesting that the activity of the NA system is determined by both genes and childhood experiences.

Depletion of NE in rodents is associated with despair and giving up behavior or learned helplessness.

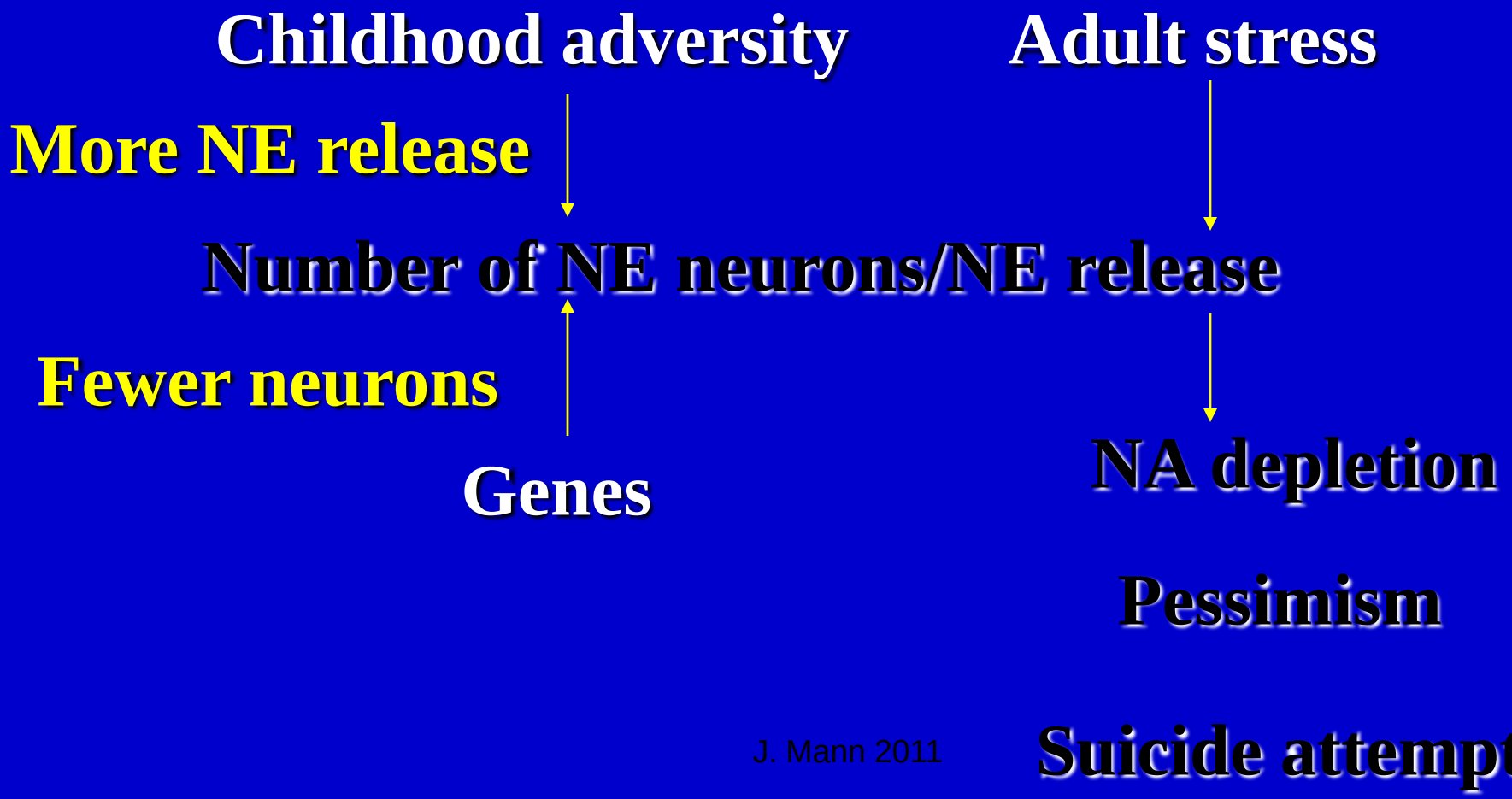
- Childhood abuse results in excessive NE release after a laboratory stress in adulthood. Such excessive NE release may lead to NE

Figure 1: Time to suicide attempt* or death and CSF MHPG level



Galfalvy et al 2005

Noradrenergic Stress Response System



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Summary

- Clinical and biological predictors of risk for suicidal behavior are needed.
- Risk is determined by childhood experience and genes and their interaction.
- Prevention requires diagnosis of major psychiatric disorders and detection of those with diathesis.
- Both stressors and diathesis are predictors of suicidal behavior and treatment/prevention targets.

Acknowledgements

- Postmortem studies: Victoria Arango, Gorazd Rosoklija, Andrew Dwork, Duma Aleksej and Mark Underwood
- Clinical Studies: Maria Oquendo, Ainsley Burke, Barbara Stanley, Dianne Currier, David Brent and lots of others
- Brain Imaging: Ramin Parsey, Todd Ogden, Dileep Kumar, Matthew Milak, Elizabeth Sublette, Jeff Miller and lots of others.
- Statistics: Steve Ellis, Hanga Galfalvy
- Genetics: Yung-yu Huang, Joe Terwilliger, Victoria Haghighi, Gil Zalsman and Jim Russo
- Gene Expression and morphometry: Victoria Arango, Alona Bach Mizrachi, Maura Boldrini, Suham Kassir and lots of others.