Ψυχική ανθεκτικότητα και βιολογικοί μηχανισμοί

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Επισκόπηση

RESILIENCE

BIOLOGICAL MECHANISMS

ΨΥΧΙΚΗ ΑΝΘΕΚΤΙΚΟΤΗΤΑ (RESILIENCE)

Τι είναι η ψυχική ανθεκτικότητα;

- Βασική ορολογία.
  - Resilience
  - Προϋποθέσεις για να γίνει λόγος για ψυχική ανθεκτικότητα
  - Προστατευτικοί παράγοντες (Protective factors)
  - Προωθητικοί παράγοντες (Promotive factors)
  - Παράγοντες κινδύνου (Risk factors)

Τι είναι η ψυχική ανθεκτικότητα;

Γνωρίζετε τον όρο;

Τι περιγράφει;

Μερικά παραδείγματα

Tiffany Wright

Yusra Mardini: 2017 UNHCR Goodwill Ambassador (check also: https://www.yusra-mardini.com/)

Nadia Murad: Winner of the 2018 Nobel Peace Prize winner for fighting sexual violence against women.

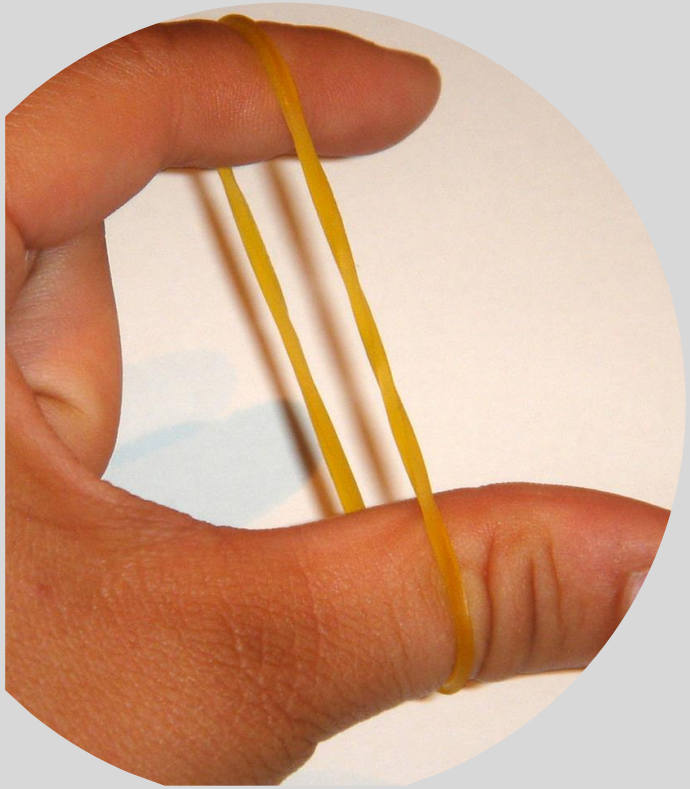
Στέφανος Μαστροθεόδωρος, Μεταπτυχιακό Πρόγραμμα "Ψυχολογία" - Ειδίκευση: "Εφαρμοσμένη Αναπτυξιακή Ψυχολογία", Πάντειο Πανεπιστήμιο, Αθήνα

Real-life resilience

What do these stories have in common?

Can you think of similar (but not necessarily so extreme!) cases of people you know?

Definition of Resilience



Etymology: the capacity to bounce back. Like a rubber band.

The ability to withhold stress, or to return to the previous balance after the stress is gone.

Definition of Resilience

Etymology: the capacity to bounce back. Like a rubber band.

The ability to withhold stress, or to return to the previous balance after the stress is gone.

"The capacity of a dynamic system to successfully adapt to disturbances that threaten system function, viability or development." (Masten, 2014, p. 10).

TABLE 1 Depiction of a population of adolescents

	Low risk	High risk
Positive outcome	A (normative development)	B (resilience theory)
Negative outcome	C (inadequate risk assessment)	D (risk models)

Definition of resilience

- Fergus & Zimmerman, 2005 (p.400).

Key Terms in Resilience Research (I)

1. Defining adjustment:
   - Competence
   - Developmental Tasks
2. Threatening adjustment:
   - Risk
   - Cumulative Risk
3. Boosting adjustment:
   - Assets
   - Resources

--> Dimensional nature of risks/assets/resources!

Key Terms in Resilience Research (II)

Ways that risk and assets/resources relate to each other:

- Protective Factors
- Promotive Factors
- Developmental Cascades (equifinality; multifinality)

Wave 1 of Resilience Research

- Gradual change in focus: from negative to positive.
  - From:
    - Who gets sick?
    - Why?
    - What can we do to reduce sickness?
  - To:
    - Who stays well?
    - How?
    - What can we do to promote and protect health?

Wave 1 of Resilience Research

- Focus on the individual characteristics
  - “invulnerable” children
- Resilience as an inferential construct: “Preconditions” to judge resilience
- Risk as a population term
- Competence
- Controversies defining resilience
- Difficulties in judging a factor as risk, or promotive/protective.

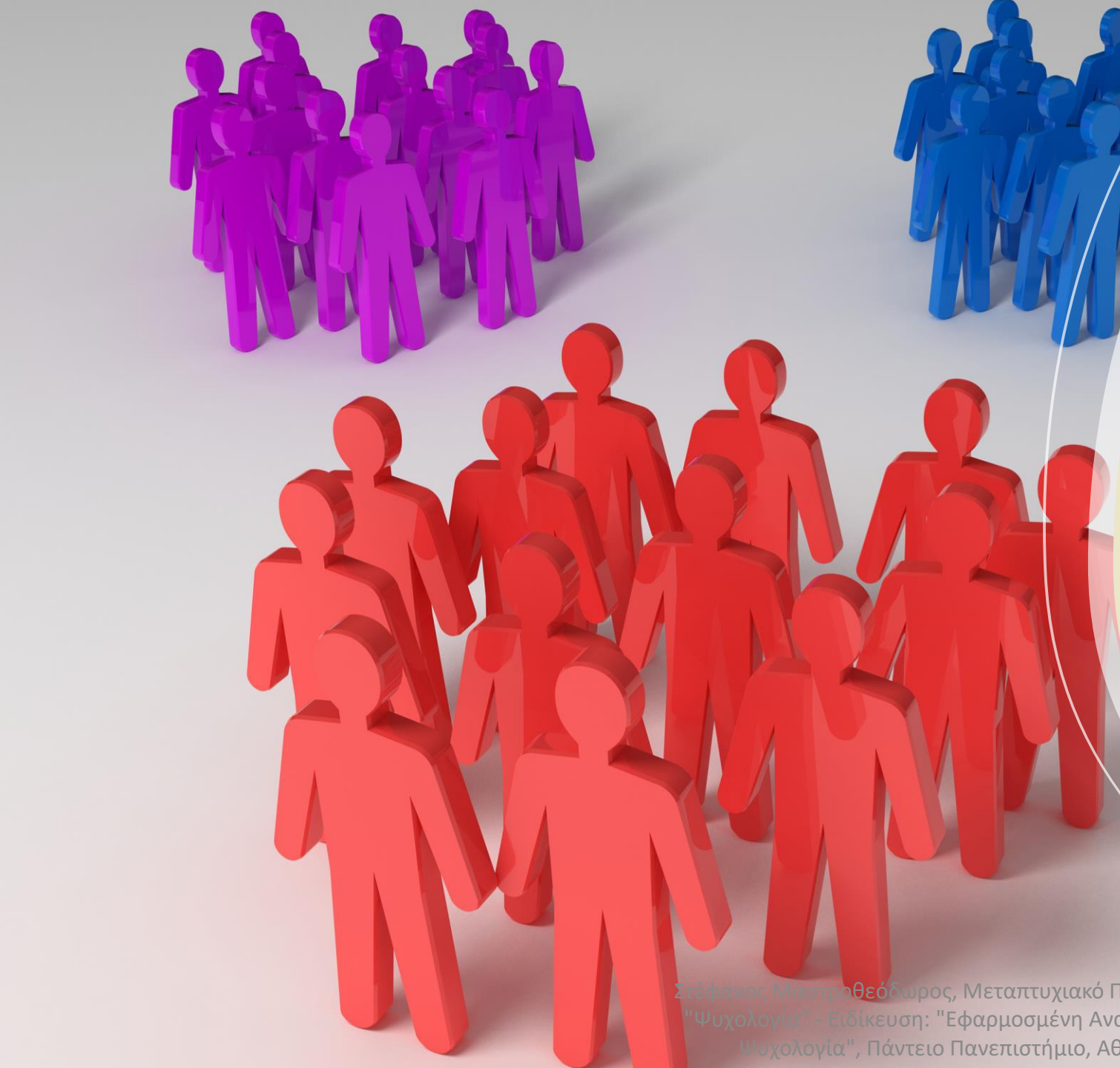
→ the short list.

Wave 2 of Resilience Research

- Emphasis on processes, mechanisms, & context.
- Contextual issues, more dynamic models.
- Integration of biological, social, and cultural processes.
- Shift from focus on individual, to focus on context (e.g., family, community, school etc).
- Realization that many of the protective and promotive factors facilitate adaptation in both high-risk and low-risk conditions → basic human adaptive systems. → “Ordinary Magic” (Masten, 2001).

Wave 2 of Resilience Research

- More complex questions, the role of the context: e.g., results of the Chicchetti & Rogosch (1997) study of maltreated children.
- Resilient pathways: a resilient pattern at one timepoint does not guarantee a steady resilient pattern across development.
- Turning points: positive adaptation might be restored if the fundamental underlying adaptive systems are restored.
- Stronger support for developmental continuity of maladaptation when multiple areas of competence have been affected.



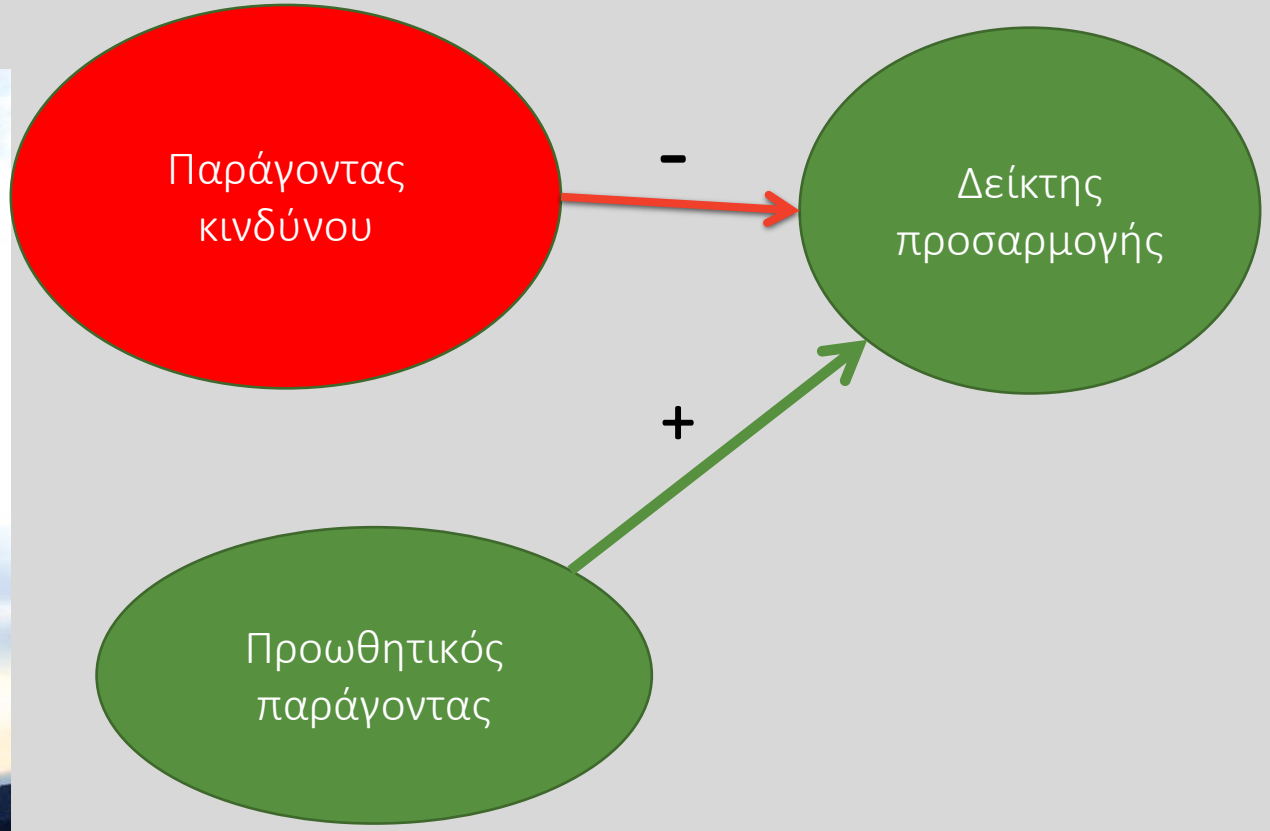
Wave 3 of Resilience Research

- Intervening to “create” resilience.
- Interventions as a way to test theory-driven hypotheses.
- Experimental studies.

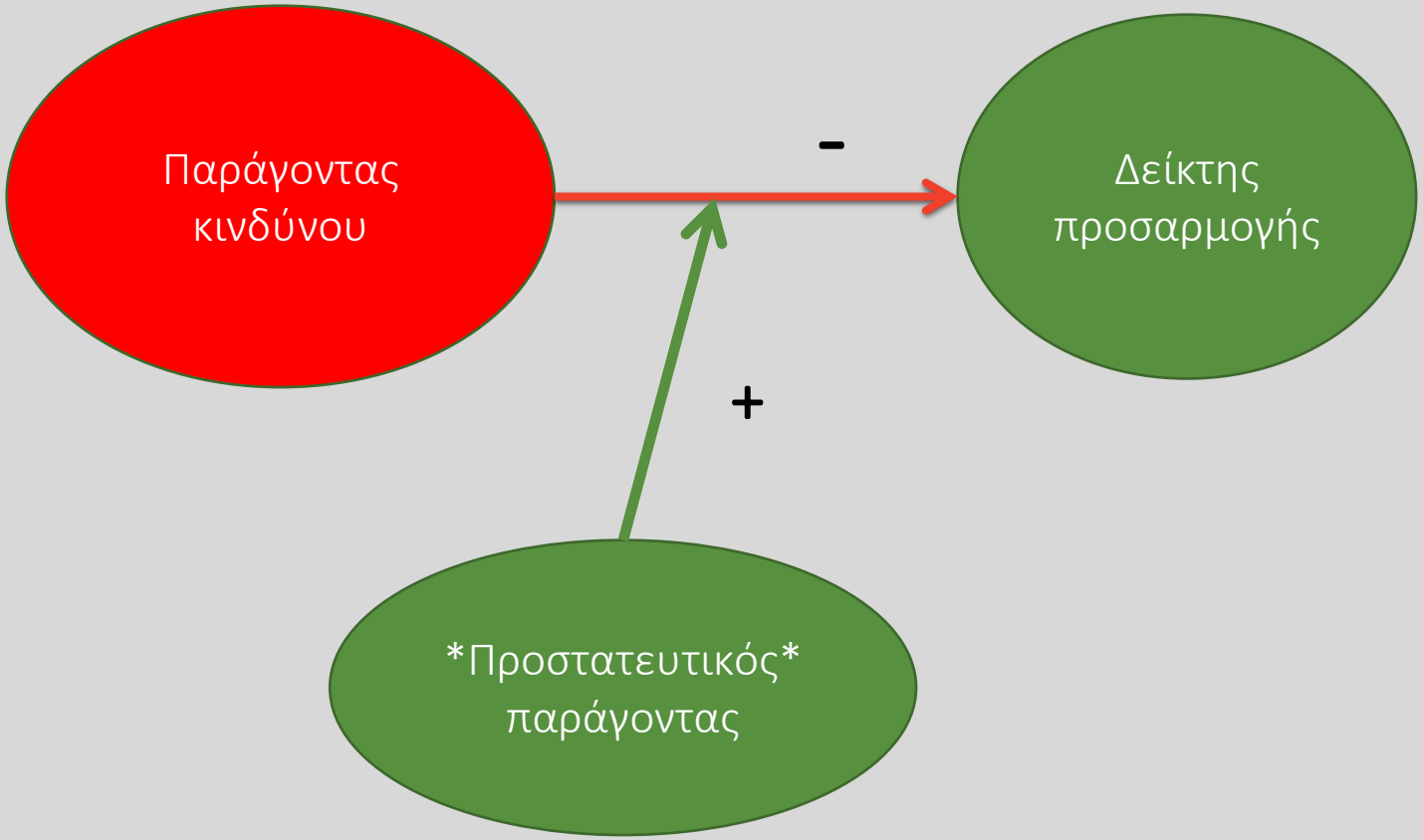
Wave 4 of Resilience Research

- Multilevel dynamics, incorporating genes, neurobiological, behavioral, and contextual systems.
- The emergence of new methods (e.g., to study genes, the brain, to model growth etc) made this wave possible.

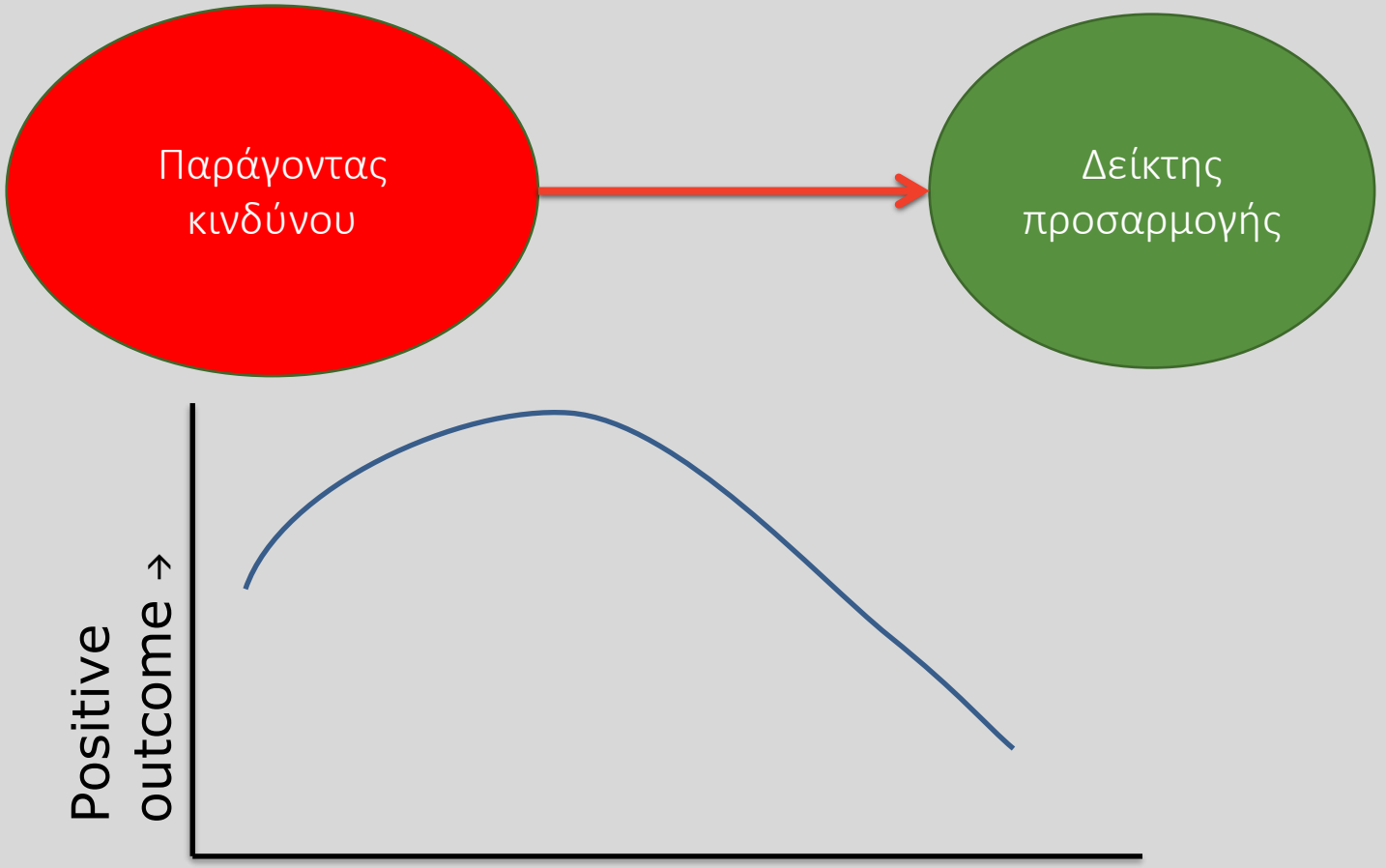
Models of Resilience - Αντιστάθμιση

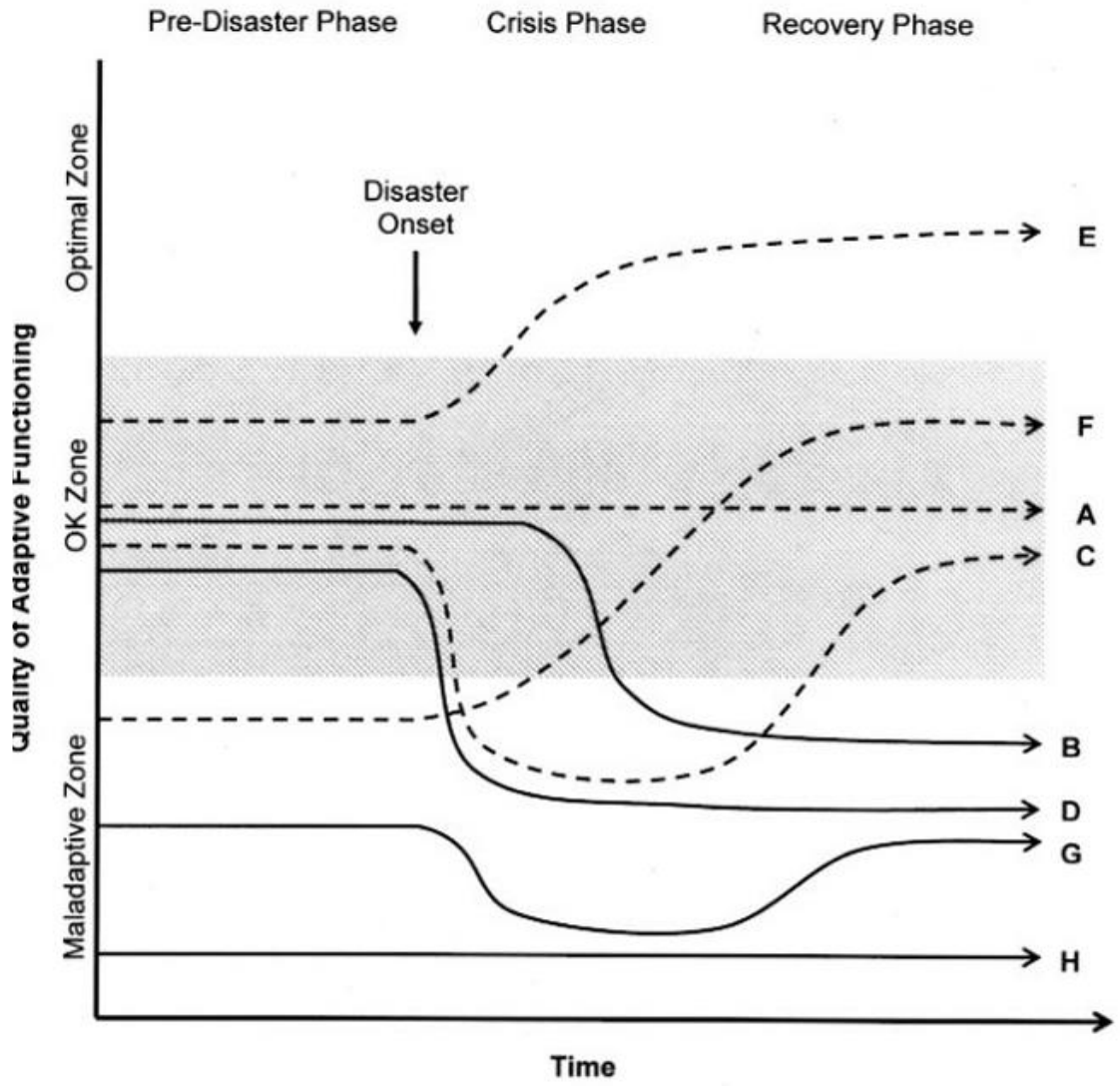


Models of Resilience - Προστασία



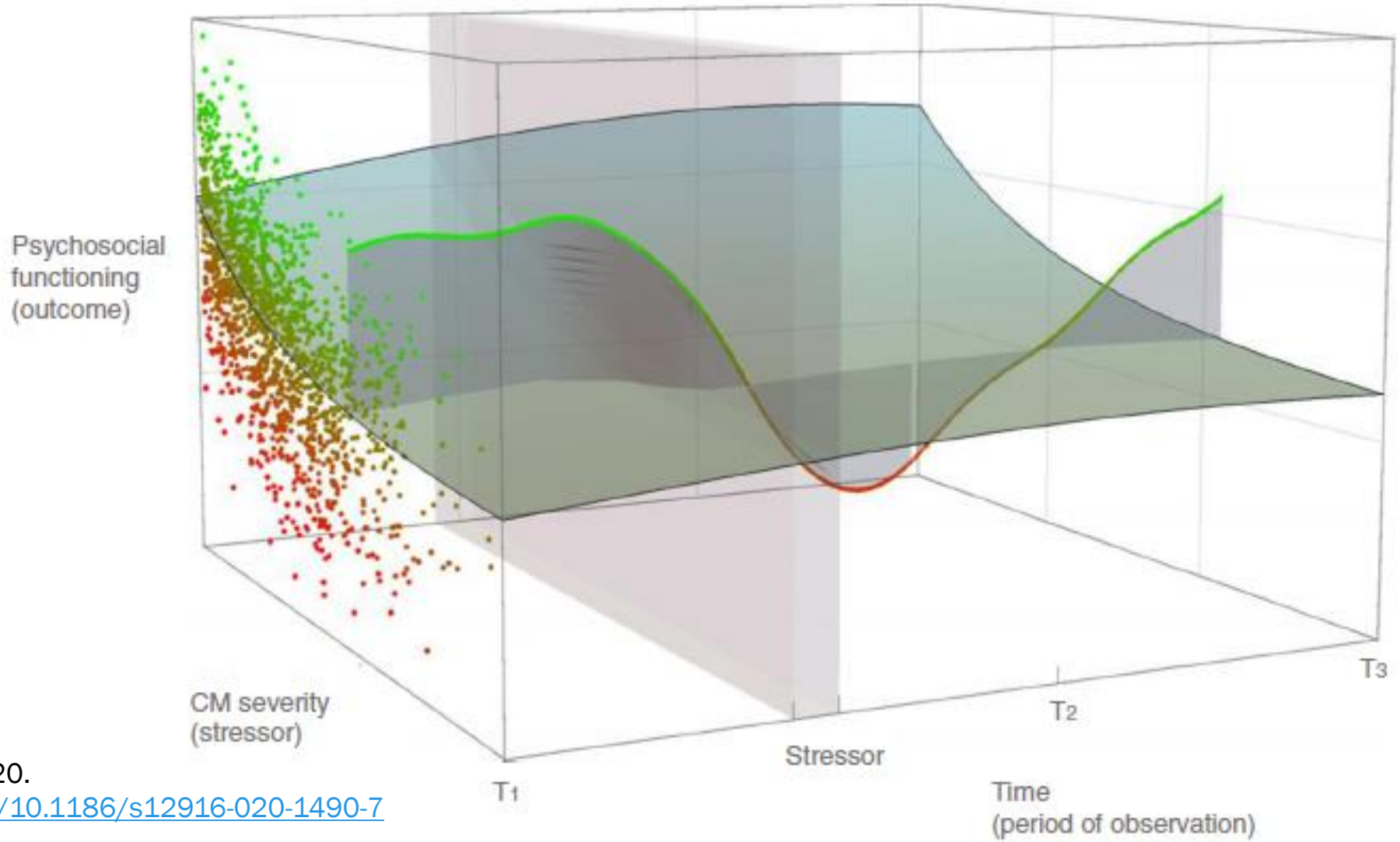
Models of Resilience – «Εμβολιασμός»





Patterns of Resilient Adaptation

1. Invulnerable: no change in level of adaptation under risk.
2. Trauma and Recovery: decline in adaptation, but recovery later on.
3. Normalization: Recovery from chronic stress (e.g., Romanian adoptees).
4. Post-traumatic Growth: Achieving even better adjustment after stress, compared to before stress. → The least studied pattern.



Ioannidis et al., 2020.
Doi: https://doi.org/10.1186/s12916-020-1490-7

Fig. 3 Trajectory of a complex resilience system in phase space. Resilience hyperplane plot of simulated data of childhood maltreatment (CM) severity (x-axis: stressor variable), psychosocial functioning (y-axis: outcome variable) and time (z-axis: period of observation), created by fitting a polynomial regression surface determined by numerical predictors of x, y and z using local fitting. An individual trajectory was hypothesised to demonstrate a complex system trajectory above and below the regression plane. Data points above the hyperplane (green) characterise 'resilient functioning', whereas all data points below the hyperplane (red) characterise non-resilient functioning at any time point (cross-sectionally)

Παράγοντες Ανθεκτικότητας	Προσαρμοστικά Συστήματα
Αποτελεσματική γονικότητα (parenting) & παροχή φροντίδας	Δεσμός. Οικογένεια
Στενές υποστηρικτικές σχέσεις με άλλους ενήλικες	Δεσμός. Κοινωνικά δίκτυα
Στενοί φίλοι και ρομαντικοί σύντροφοι	Δεσμός. Οικογενειακό σύστημα. Συνομήλικοι.
Νοημοσύνη και δεξιότητες επίλυσης προβλημάτων	Κεντρικό Νευρικό Σύστημα, μηχανισμοί μάθησης.
Αυτοέλεγχος, συναισθηματική ρύθμιση, προνοητικότητα	ΚΝΣ, συστήματα ελέγχου.
Κίνητρο επιτυχίας	Κίνητρο επίτευξης (mastery motivation). Συστήματα ανταμοιβής
Αυτοαποτελεσματικότητα (self-efficacy)	Κίνητρο επίτευξης (mastery motivation)
Πίστη, ελπίδα, πεποίθηση ότι η ζωή έχει νόημα	Θρησκευτικά και πολιτισμικά συστήματα πεποιθήσεων.
Αποτελεσματικά σχολεία	Εκπαιδευτικά συστήματα.
Αποτελεσματικές γειτονιές, αίσθηση κοινότητας, κοινοτικής αυτοαποτελεσματικότητας	Κοινότητες.

The Shortlist of Resilience Factors

Παράγοντες που έχουν βρεθεί να προστατεύουν έναντι του κινδύνου ή να προωθούν την ανθεκτικότητα.

Προσαρμογή από:

Masten, A. S. (2015). *Ordinary Magic: Resilience in Development*. New York: Guilford Press.

ISBN 978-1-4625-2371-9

Βασικό μήνυμα:

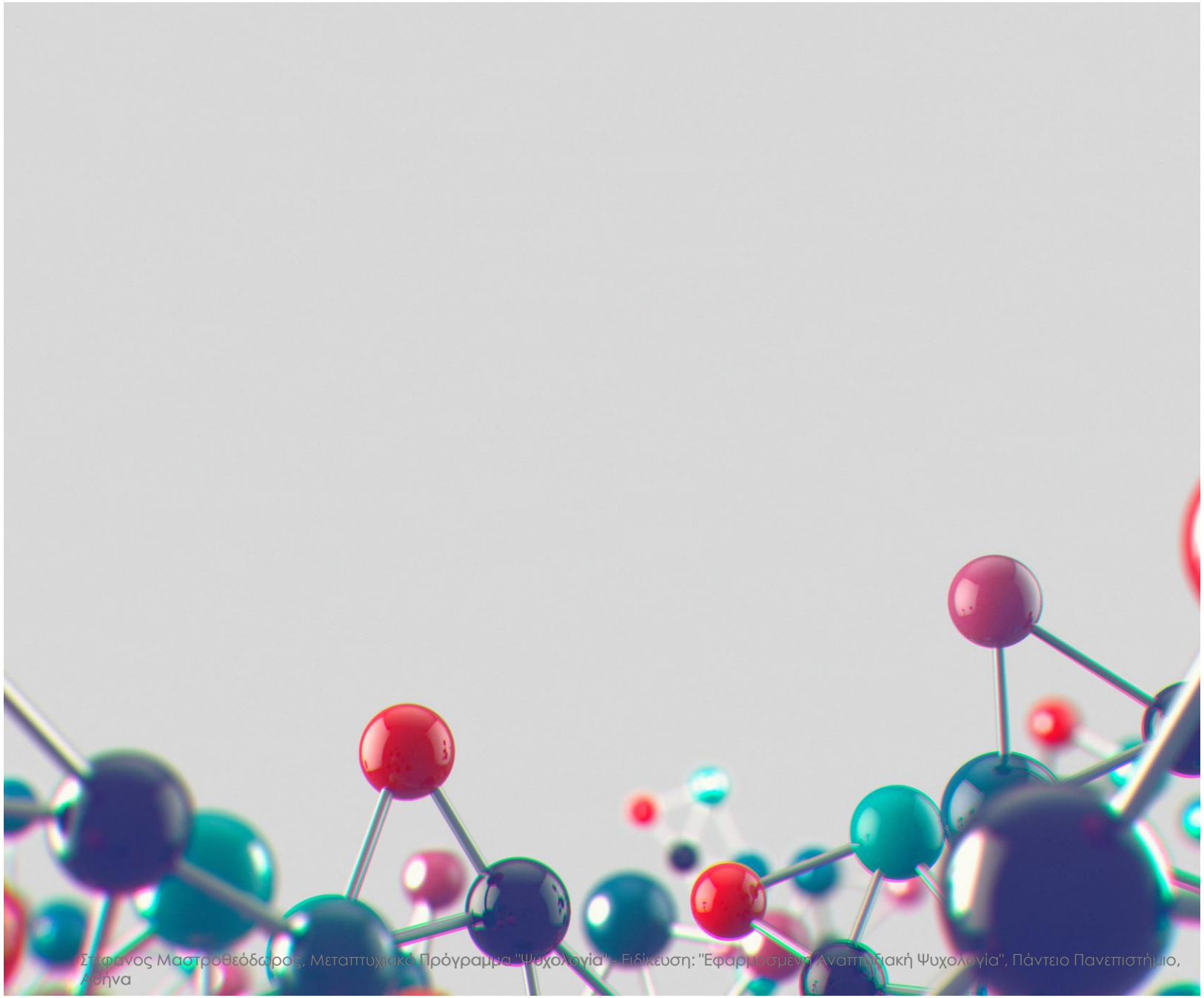
Η ψυχική ανθεκτικότητα είναι κάτι κοινό

(Ordinary Magic)

Masten, 2015

Why study resilience?

- Looking only at risk does not provide the full picture
- Risk cannot always be avoided or reduced
- Children are increasingly exposed to risk or adversity
- Knowledge about resilience can greatly improve interventions or preventions



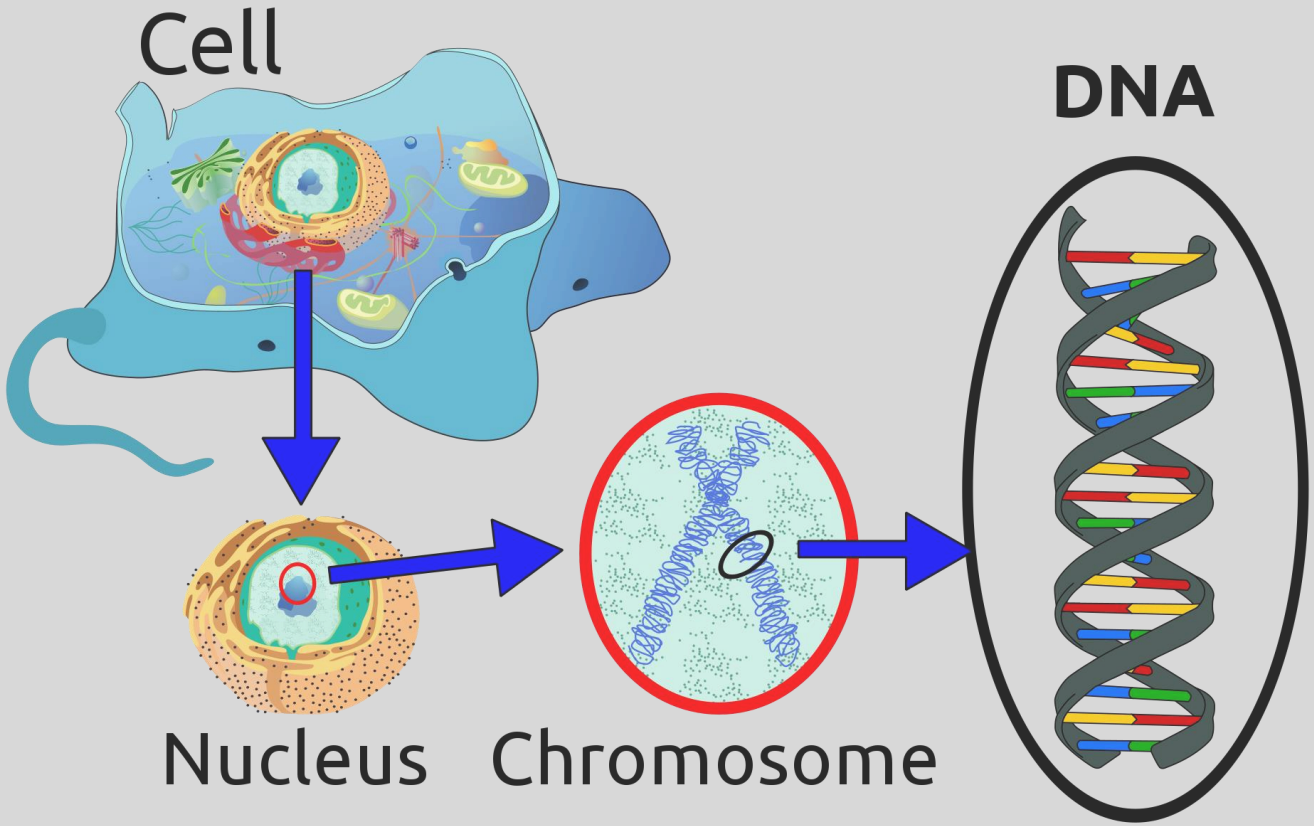
(epi-)Genetic studies

Do genetic and epigenetic factors play a role in risk and resilience?

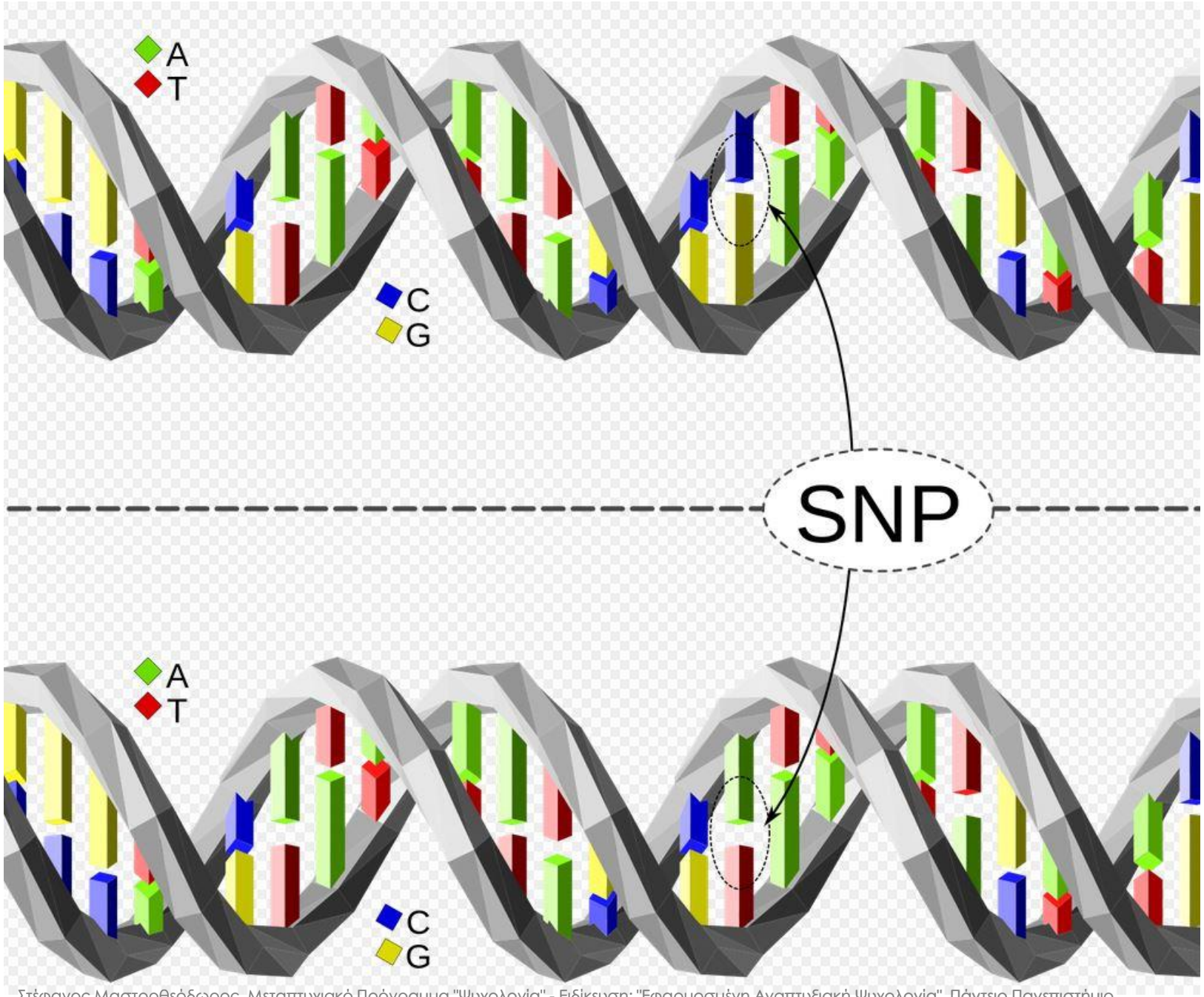
Genetic studies: focus on ***stable*** individual differences on DNA.

Epigenetic studies: focus on differences in ***varying*** gene expression.

Genetic material



Overview of the DNA

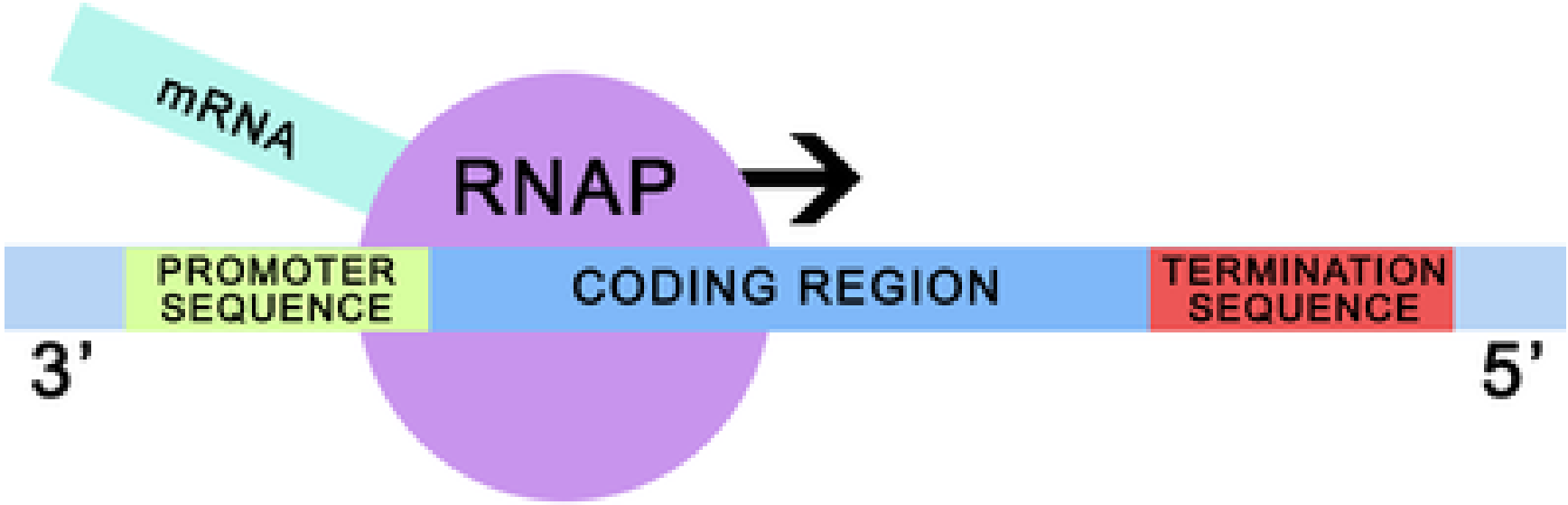


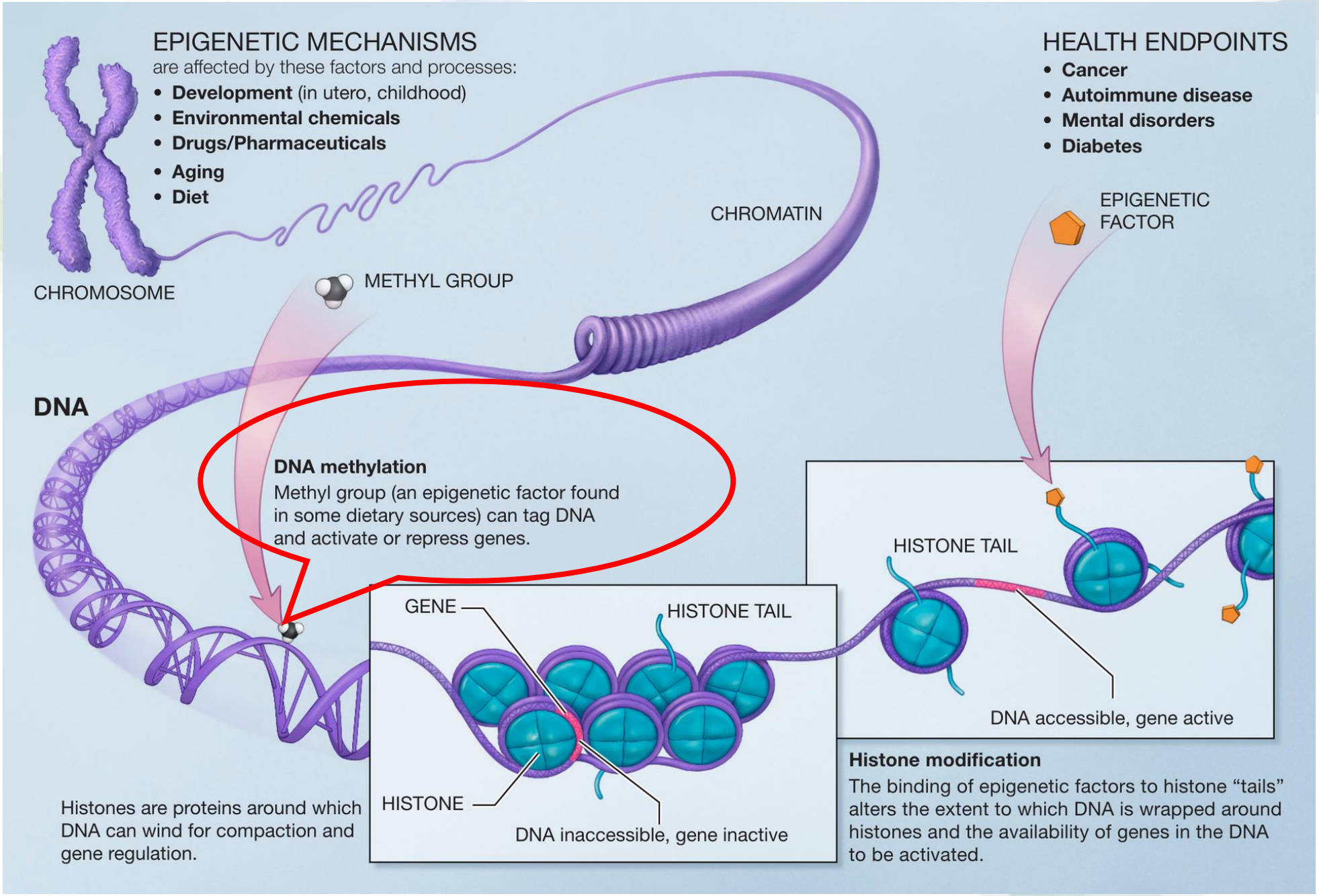
DNA – Single Nucleotide Polymorphisms (SNPs)

Photo taken from Wikipedia.org

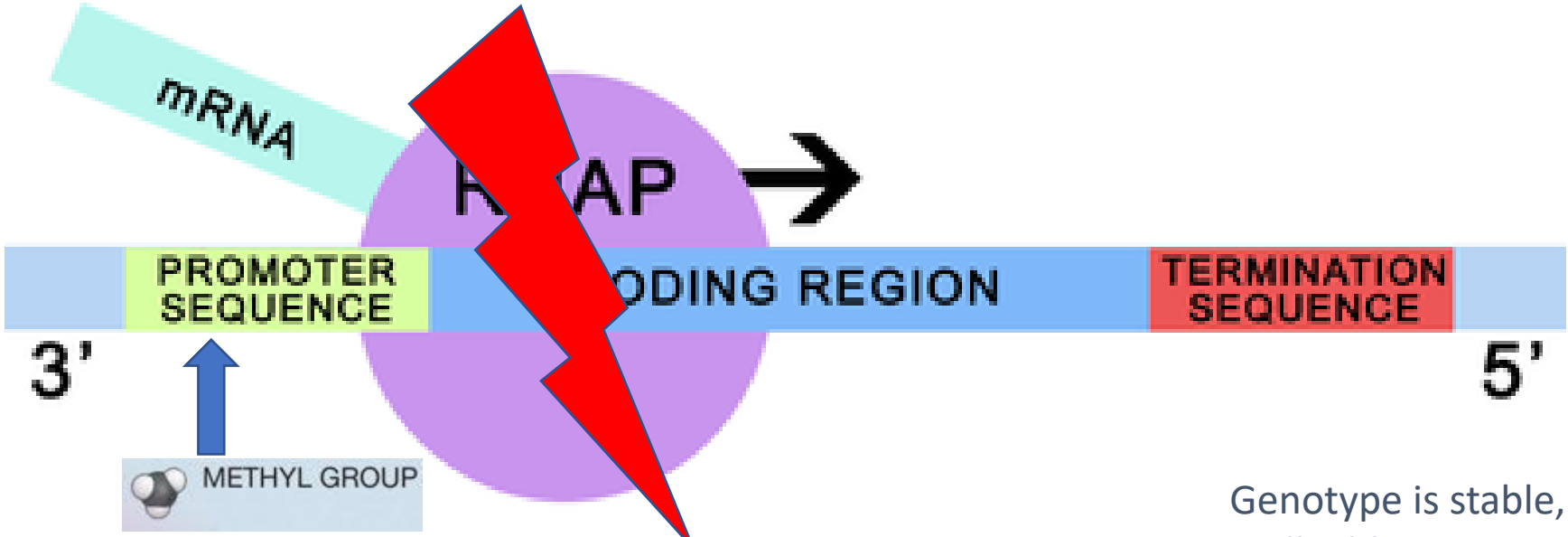
Author: David Eccles (Gringer)

DNA Transcription




EPIGENETIC MECHANISMS
are affected by these factors and processes:
• Development (in utero, childhood)
• Environmental chemicals
• Drugs/Pharmaceuticals
• Aging
• Diet
HEALTH ENDPOINTS
• Cancer
• Autoimmune disease
• Mental disorders
• Diabetes
CHROMOSOME
CHROMATIN
METHYL GROUP
EPIGENETIC FACTOR
DNA
DNA methylation
Methyl group (an epigenetic factor found in some dietary sources) can tag DNA and activate or repress genes.
GENE
HISTONE TAIL
HISTONE
DNA inaccessible, gene inactive
HISTONE TAIL
DNA accessible, gene active
Histones are proteins around which DNA can wind for compaction and gene regulation.
Histone modification
The binding of epigenetic factors to histone "tails" alters the extent to which DNA is wrapped around histones and the availability of genes in the DNA to be activated.

DNA Transcription



On specific Cytosine-phosphate-Guanine (CpG) sites.

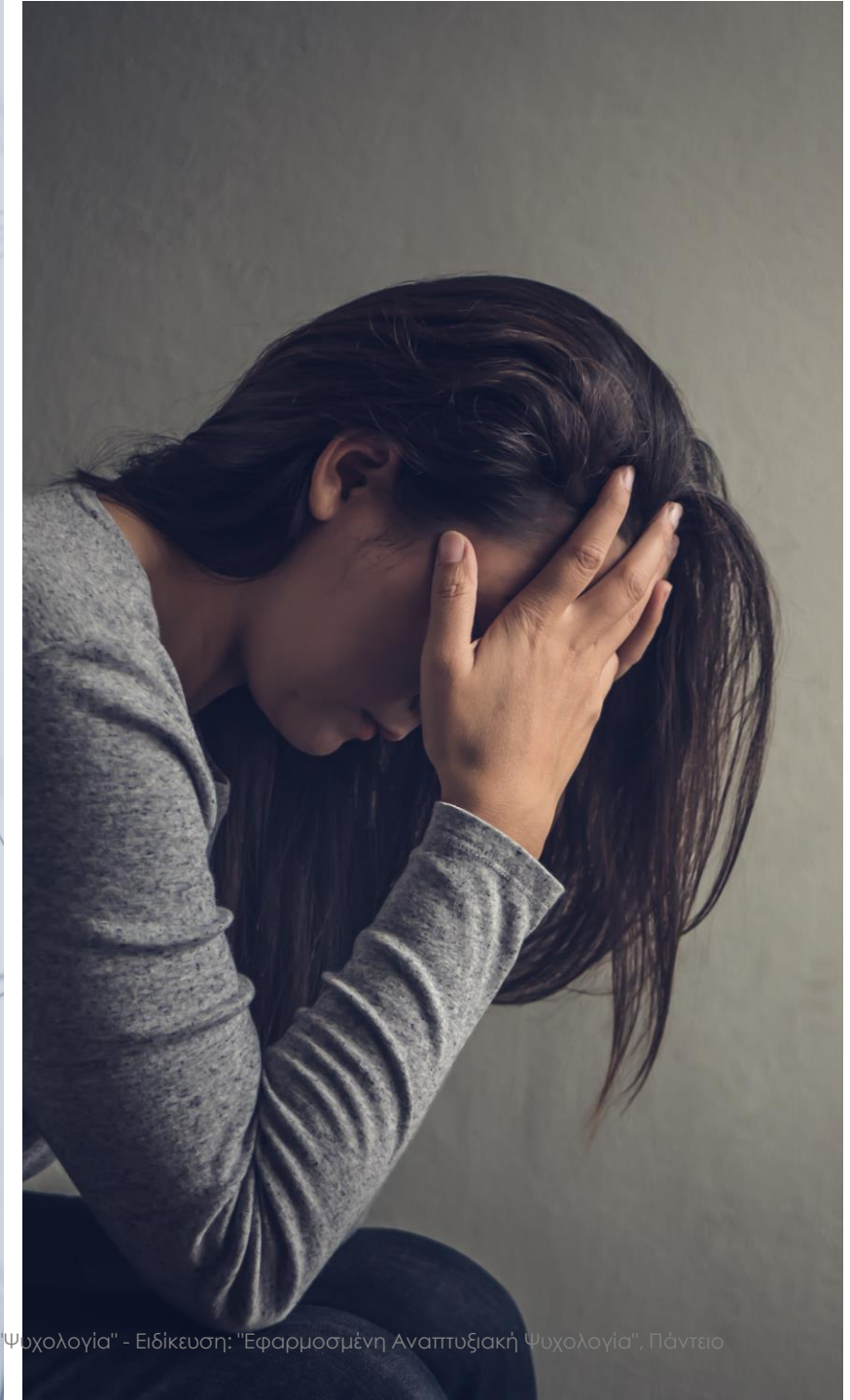
Genotype is stable, but the epigenome is malleable.

Differential sensitivity to experience

- Variability in responsiveness
- “For better and for worse”.
- Protective factors defined functionally, not in absolute terms.
- Sensitivity might be susceptible to (early) experiences.

Pluess, 2015; Child Development Perspectives,

http://doi.wiley.com/10.1111/cdep.12120



Polygenic Risk for Major Depression Interacts with Parental Criticism in Predicting Adolescent Depressive Symptom Development

Nelemans, Boks, Lin, et al., 2020.

https://doi.org/10.1007/s10964-020-01353-4

Journal of Youth and Adolescence
https://doi.org/10.1007/s10964-020-01353-4

EMPIRICAL RESEARCH

Polygenic Risk for Major Depression Interacts with Parental Criticism in Predicting Adolescent Depressive Symptom Development

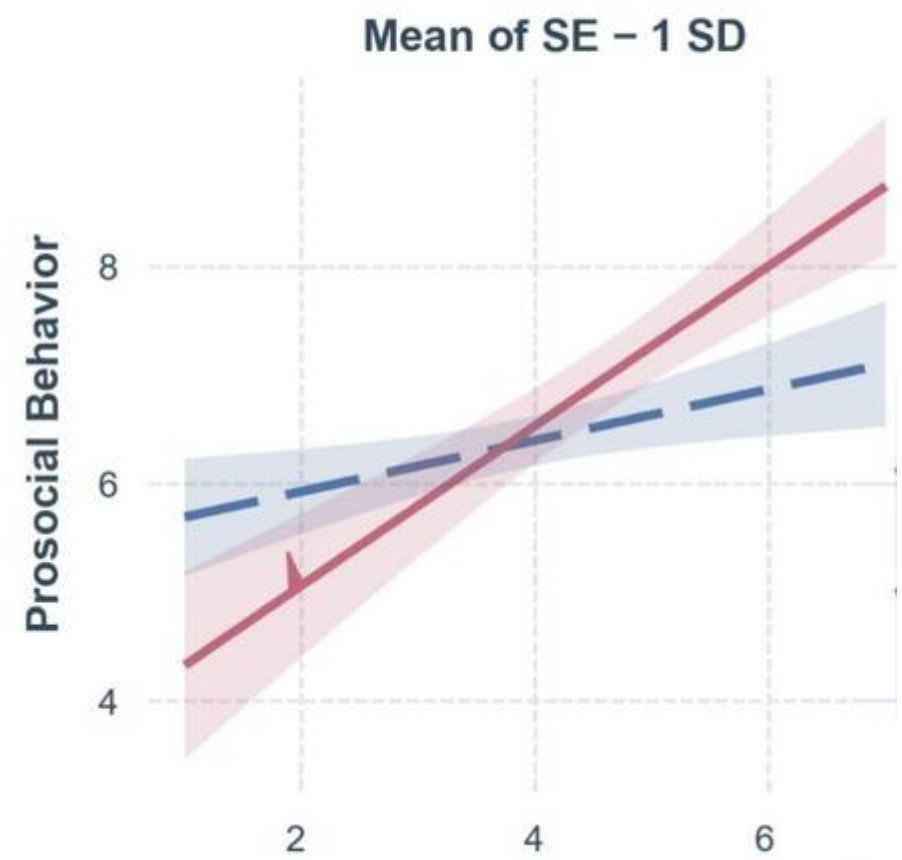
Stefanie A. Nelemans[1] · Marco Boks[2] · Bochao Lin[3] · Tineke Oldehinkel[4] · Pol van Lier[5] · Susan Branje[1] · Wim Meeus[1,6]

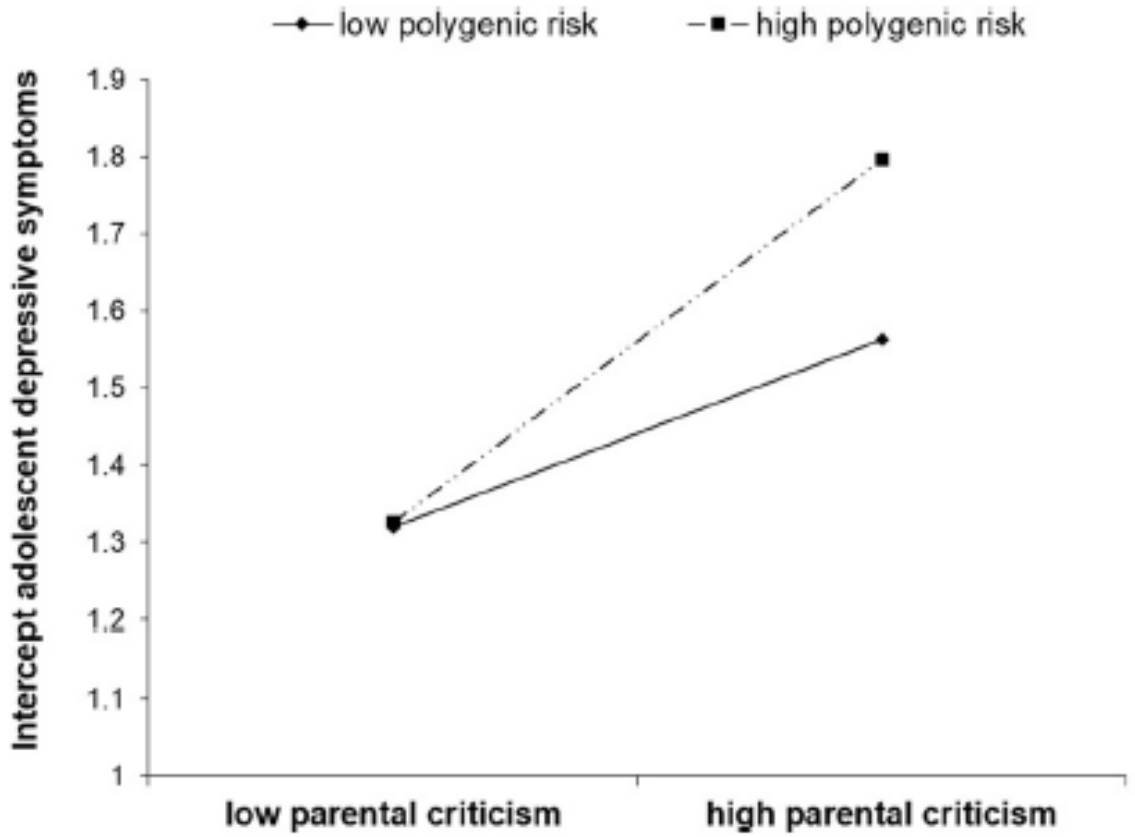
Received: 29 June 2020 / Accepted: 2 November 2020

Polygenic Risk for Depression

- Background:
  - Increasing interest in GxE studies explaining depression.
  - Depressive symptoms as a continuous distribution; different degrees of severity in the general population.
  - Lack of longitudinal studies.
  - MDD as moderately heritable.
  - Polygenic etiology.
  - Move of the field: from *candidate gene approach* to the *polygenic approach*.
  - Environmental stress in the development of depression.
  - Two competing hypotheses: Diathesis-Stress vs Differential Susceptibility
- Aims
  - Investigate interactions between genetic vulnerability with environmental stress in predicting depressive symptom development.

Diathesis-Stress vs Differntial Susceptibility





Polygenic Risk for Depression and Parental Criticism

- Method
  - Polygenic risk score: the additive weighted effect of multiple genetic loci – Single Nucleotide Polymorphisms (SNPs) – detected in large-scale studies that examine large parts of the genome.
  - E.g., 17 independent SNPs contributing to depression.
  - 12 Alternative PRS based on gradually more lenient thresholds, from $p < 5x10e-8$ (17 SNPs) to $p < 5x10e-2$ (5,5013 SNPs) to $p = .50$ (342,808 SNPs).
  - Longitudinal data on depressive symptoms → Latent Growth Curve Models.

Polygenic Risk for Depression and Parental Criticism - Results

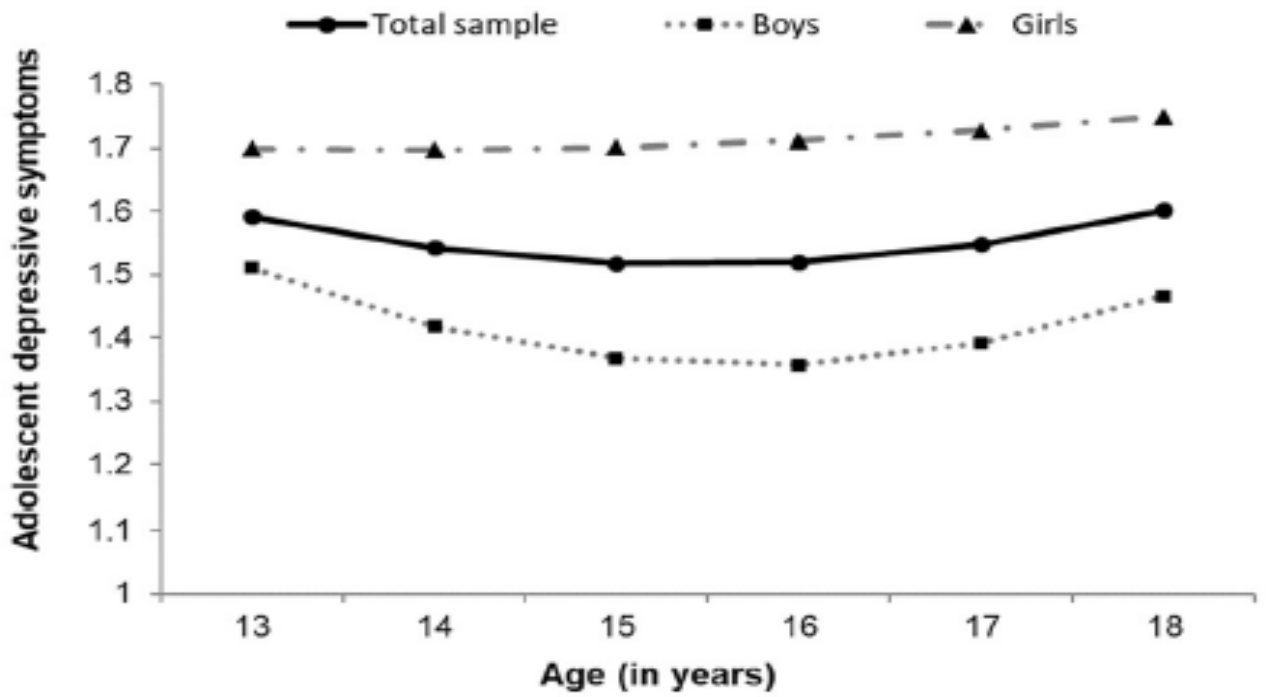


Fig. 1 Graphical representation of adolescent depressive symptom development from early to late adolescence across six successive waves (i.e., approximately ages 13–18 years) for the total sample ($N = 327$), as well as boys ($n = 184$) and girls ($n = 143$) separately

Polygenic Risk for Depression and Parental Criticism - Results

Table 3 Summary of standardized coefficients of polygenic risk for MDD predicting adolescent depressive symptom development, controlling for sex ($N = 327$)

Model	Intercept[a]	Linear slope	Quadratic slope
PRS MDD 5×10^{-8}[b]	$\beta = \mathbf{0.17}$, $p = \mathbf{0.019}$	$\beta = 0.08$, $p = 0.412$	$\beta = -0.10$, $p = 0.324$
PRS MDD 5×10^{-7}	$\beta = \mathbf{0.13}$, $p = \mathbf{0.038}$	$\beta = \mathbf{0.19}$, $p = \mathbf{0.022}$	$\beta = \mathbf{-0.18}$, $p = \mathbf{0.041}$
PRS MDD 5×10^{-6}	$\beta = 0.09$, $p = 0.159$	$\beta = \mathbf{0.21}$, $p = \mathbf{0.018}$	$\beta = \mathbf{-0.20}$, $p = \mathbf{0.034}$
PRS MDD 5×10^{-5}	$\beta = 0.12$, $p = 0.083$	$\beta = 0.15$, $p = 0.127$	$\beta = -0.12$, $p = 0.236$
PRS MDD 5×10^{-4}	$\beta = \mathbf{0.13}$, $p = \mathbf{0.043}$	$\beta = 0.08$, $p = 0.435$	$\beta = -0.05$, $p = 0.631$
PRS MDD 5×10^{-3}	$\beta = \mathbf{0.14}$, $p = \mathbf{0.017}$	$\beta = 0.08$, $p = 0.435$	$\beta = -0.07$, $p = 0.509$
PRS MDD 0.01	$\beta = \mathbf{0.16}$, $p = \mathbf{0.011}$	$\beta = 0.04$, $p = 0.696$	$\beta = -0.01$, $p = 0.946$
PRS MDD 0.05	$\beta = \mathbf{0.19}$, $p = \mathbf{0.002}$	$\beta = 0.07$, $p = 0.542$	$\beta = -0.05$, $p = 0.656$
PRS MDD 0.10	$\beta = \mathbf{0.19}$, $p = \mathbf{0.003}$	$\beta = 0.04$, $p = 0.711$	$\beta = -0.02$, $p = 0.842$
PRS MDD 0.20	$\beta = \mathbf{0.20}$, $p = \mathbf{0.002}$	$\beta = 0.05$, $p = 0.632$	$\beta = -0.04$, $p = 0.744$
PRS MDD 0.30	$\beta = \mathbf{0.20}$, $p = \mathbf{0.001}$	$\beta = 0.04$, $p = 0.701$	$\beta = -0.03$, $p = 0.812$
PRS MDD 0.40	$\beta = \mathbf{0.21}$, $p = \mathbf{0.001}$	$\beta = 0.06$, $p = 0.595$	$\beta = -0.05$, $p = 0.685$
PRS MDD 0.50	$\beta = \mathbf{0.21}$, $p = \mathbf{0.001}$	$\beta = 0.05$, $p = 0.654$	$\beta = -0.04$, $p = 0.729$

PRS MDD […] = polygenic risk score for major depression, calculated based on the mentioned p-value threshold. Significant main effects ($p < 0.05$) are in bold

[a]The average age of participants at the intercept was 13.00 years old ($SD = 0.44$)

[b]The PRS MDD 5×10^{-8} score was based on the meta-analysis by Hyde et al. (2016) and corrected for adolescent age, sex, and population stratification. The other 12 polygenic risk scores for major depression with different p-value thresholds were based on the 23andMe summary statistics and also corrected for adolescent age, sex, and population stratification

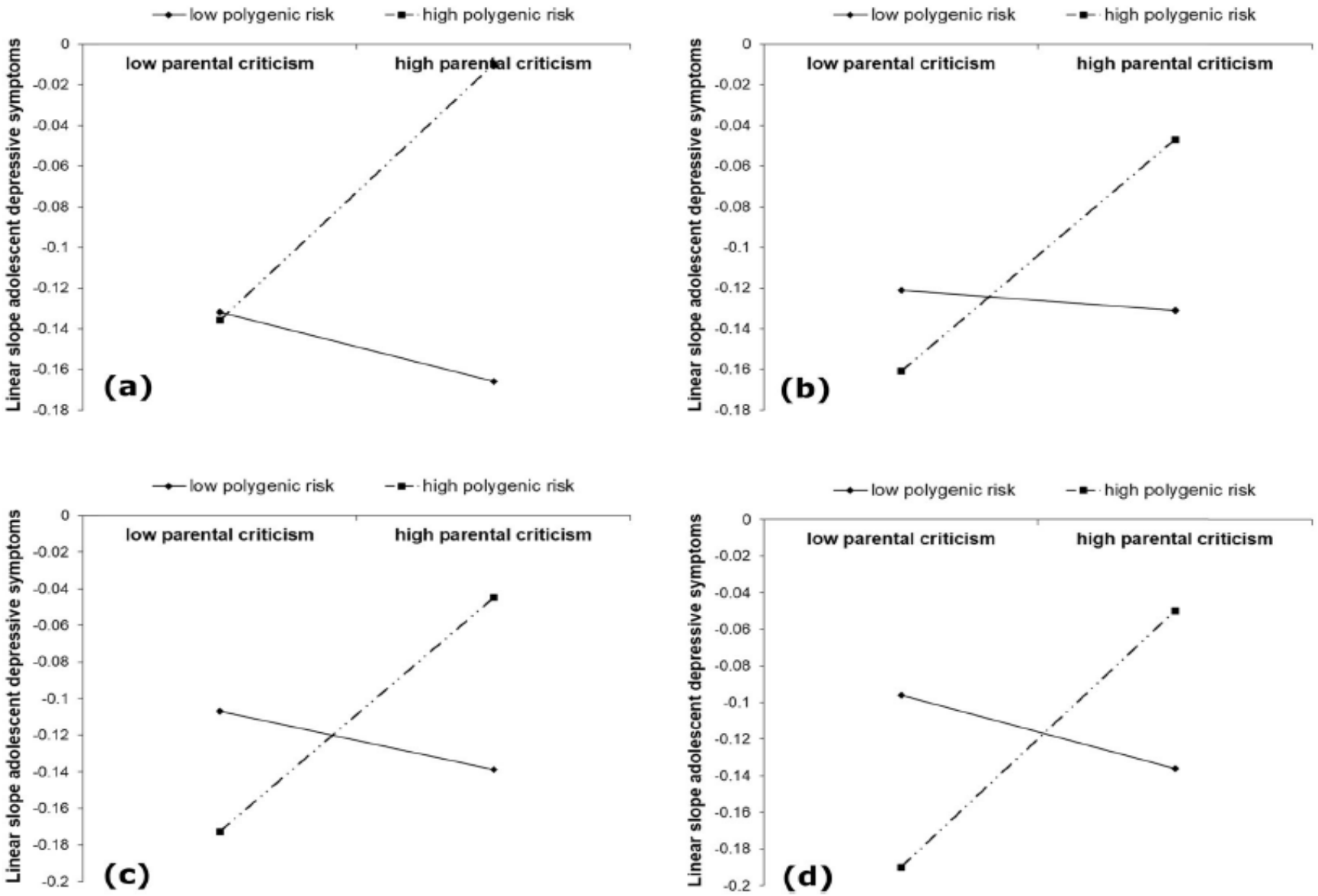
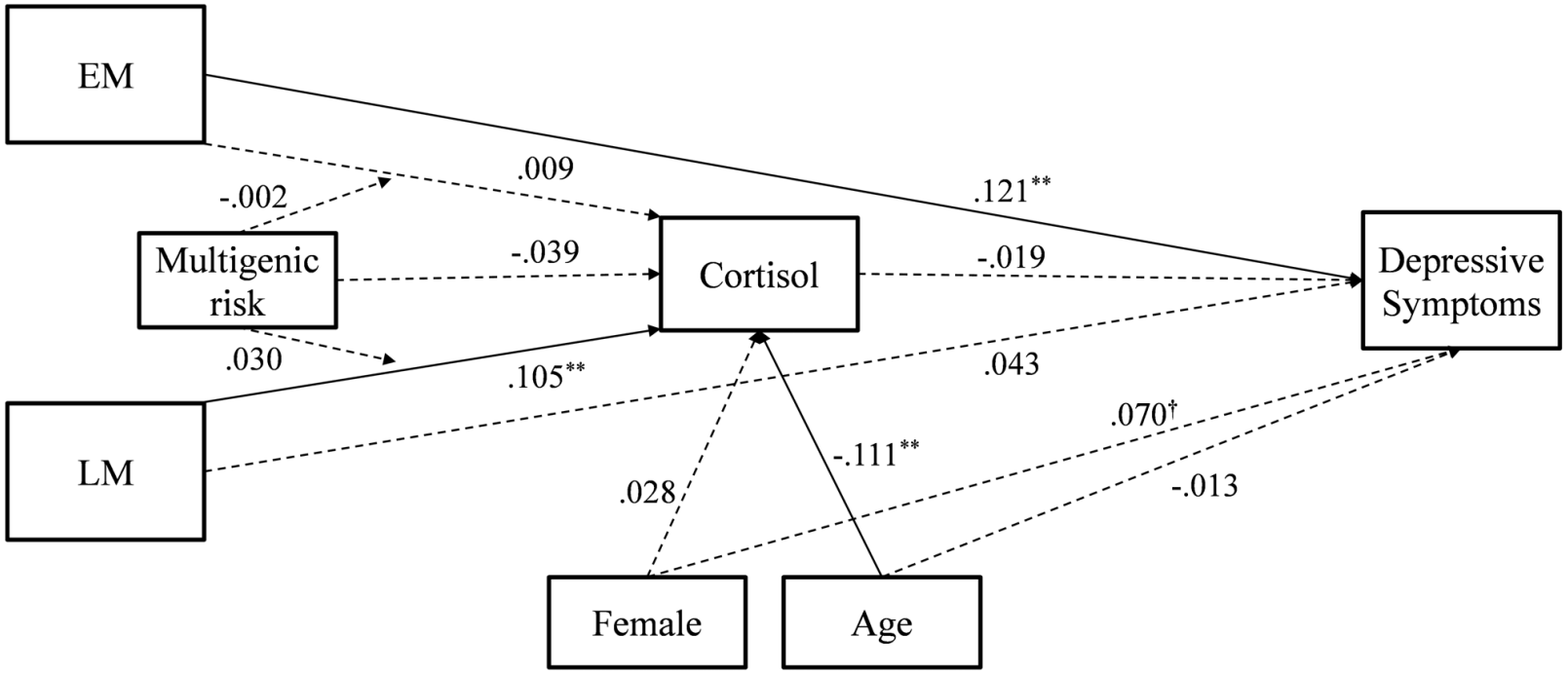


Fig. 3 Graphical representation of the significant interactions in the sensitivity analyses between the corrected polygenic risk scores for major depression and the multi-informant longitudinal index of parental criticism on linear slope levels of adolescent depressive symptoms, for p-value thresholds (**a**) $p < 5 \times 10^{-7}$, (**b**) $p < 5 \times 10^{-3}$, (**c**) $p < 0.05$, and (**d**) $p < 0.50$



Inconclusive results – More nuance needed

VanZomeren et al., 2020. Maltreatment timing, HPA axis functioning, multigenic risk, and depressive symptoms in African American youth: Differential associations without moderated mediation. https://doi.org/10.1017/S0954579420000589

Only Early-onset Maltreatment (EM, before age 5) influenced depressive symptoms.

No effects on/of cortisol or multigenic risk score.

Timing!

Stress response: Differential methylation associates with child abuse

- McGowan et al., 2009:

ARTICLES

nature neuroscience

Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse

Patrick O McGowan[1,2], Aya Sasaki[1,2], Ana C D'Alessio[3], Sergiy Dymov[3], Benoit Labonté[1,4], Moshe Szyf[2,3], Gustavo Turecki[1,4] & Michael J Meaney[1,2,5]

Stress response: Differential methylation associates with child abuse

- McGowan et al., 2009:

Maternal care influences hypothalamic-pituitary-adrenal (HPA) function in the rat through epigenetic programming of glucocorticoid receptor expression. In humans, childhood abuse alters HPA stress responses and increases the risk of suicide. We examined epigenetic differences in a neuron-specific glucocorticoid receptor (*NR3C1*) promoter between postmortem hippocampus obtained from suicide victims with a history of childhood abuse and those from either suicide victims with no childhood abuse or controls. We found decreased levels of glucocorticoid receptor mRNA, as well as mRNA transcripts bearing the glucocorticoid receptor 1_F splice variant and increased cytosine methylation of an *NR3C1* promoter. Patch-methylated *NR3C1* promoter constructs that mimicked the methylation state in samples from abused suicide victims showed decreased NGFI-A transcription factor binding and NGFI-A–inducible gene transcription. These findings translate previous results from rat to humans and suggest a common effect of parental care on the epigenetic regulation of hippocampal glucocorticoid receptor expression.

re
roscience

Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse

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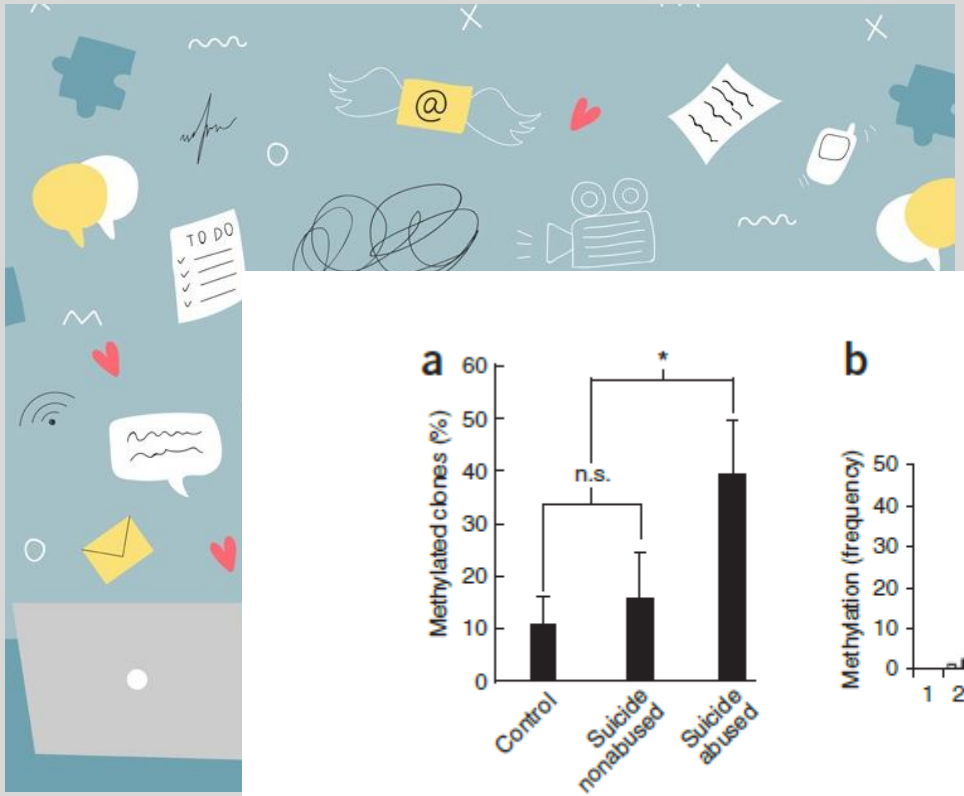
Stress response systems



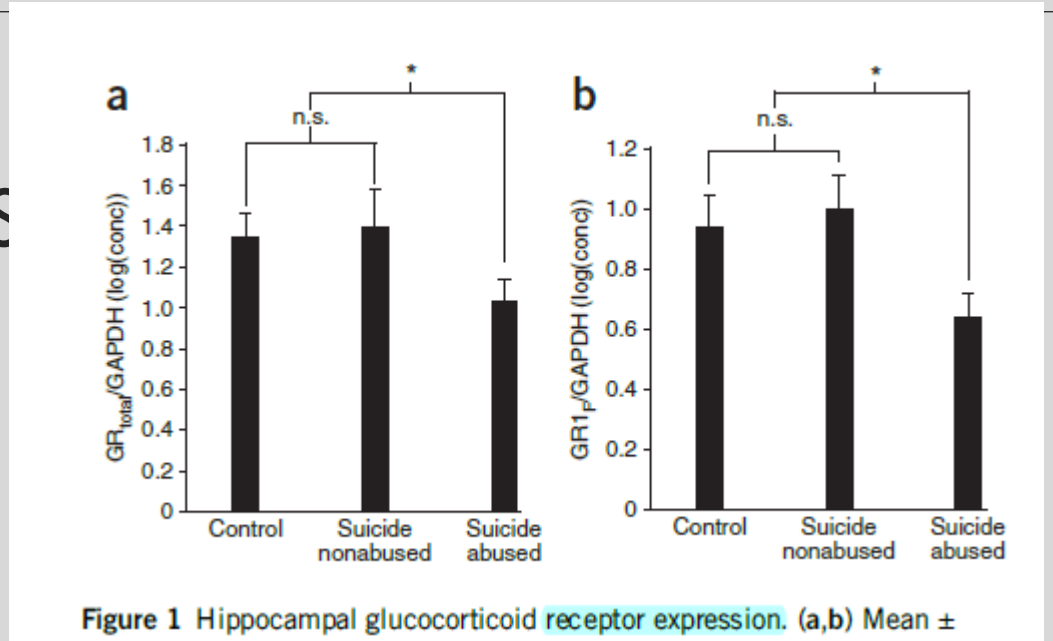


Figure 1 Hippocampal glucocorticoid receptor expression. (a,b) Mean ±

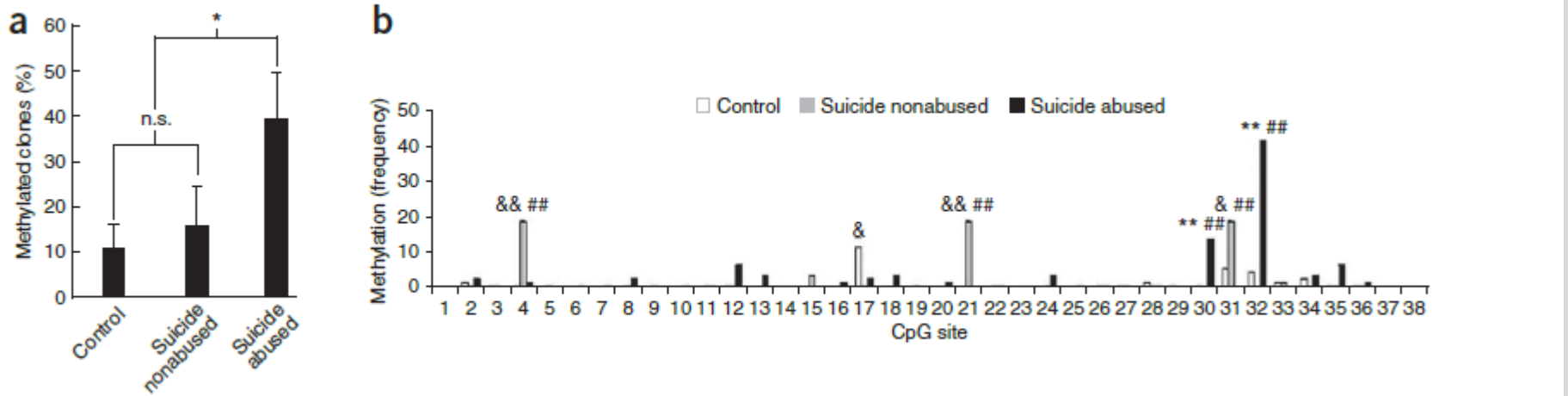


Figure 2 Methylation of the *NR3C1* promoter in the hippocampus. Twenty clones were sequenced for each subject for methylation mapping. (a) Mean ± s.e.m.

Transgenerational effects of prenatal environment – the Dutch Famine 1944-1945

Transgenerational effects of prenatal environment – the Dutch Famine 1944-1945

BJOG An International Journal of Obstetrics and Gynaecology
Royal College of Obstetricians & Gynaecologists

Volume 120, Issue 5
April 2013
Pages 548-554

Original Article | Full Access

Transgenerational effects Dutch famine

MVE Veenendaal, RC Painter, SR de Ro
Hanson, TJ Roseboom

First published: 24 January 2013 | https:/

UBU link

SECTIONS

Objective We previously showed that maternal under-nutrition during gestation is associated with increased metabolic and cardiovascular disease in the offspring. Also, we found increased neonatal adiposity among the grandchildren of women who had been undernourished during pregnancy. In the present study we investigated whether these transgenerational effects have led to altered body composition and poorer health in adulthood in the grandchildren.

Design Historical cohort study.

Setting Web-based questionnaire.

Population The adult offspring (F2) of a cohort of men and women (F1) born around the time of the 1944–45 Dutch famine.

Methods We approached the F2 adults through their parents. Participating F2 adults (n = 360, mean age 37 years) completed an online questionnaire.

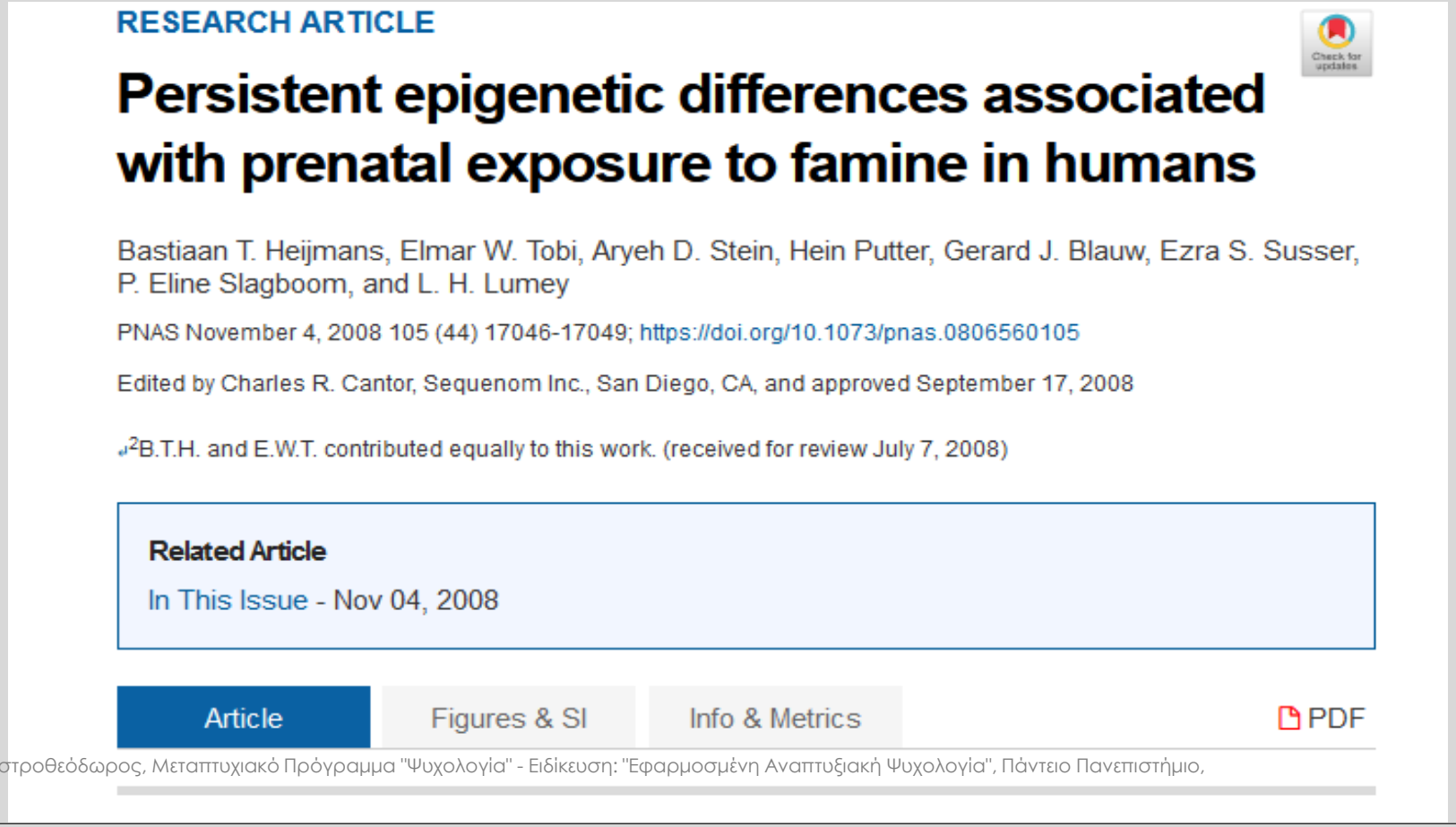
Main outcome measures Weight, body mass index (BMI), and health in F2 adults, according to F1 prenatal famine exposure.

Results Adult offspring (F2) of prenatally exposed F1 fathers had higher weights and BMIs than offspring of prenatally unexposed F1 fathers (+4.9 kg, P = 0.03; +1.6 kg/m², P = 0.006). No such effect was found for the F2 offspring of prenatally exposed F1 mothers. We observed no differences in adult health between the F2 generation groups.

Conclusions Offspring of prenatally undernourished fathers, but not mothers, were heavier and more obese than offspring of fathers and mothers who had not been undernourished prenatally. We found no evidence of transgenerational effects of grandmaternal under-nutrition during gestation on the health of this relatively young group, but the increased adiposity in the offspring of prenatally undernourished fathers may lead to increased chronic disease rates in the future.

Keywords Famine, fetal, health, transgenerational.

Transgenerational effects of prenatal environment – the Dutch Famine 1944-1945



RESEARCH ARTICLE

Persistent epigenetic differences associated with prenatal exposure to famine in humans

Bastiaan T. Heijmans, Elmar W. Tobi, Aryeh D. Stein, Hein Putter, Gerard J. Blauw, Ezra S. Susser, P. Eline Slagboom, and L. H. Lumey

PNAS November 4, 2008 105 (44) 17046-17049; https://doi.org/10.1073/pnas.0806560105

Edited by Charles R. Cantor, Sequenom Inc., San Diego, CA, and approved September 17, 2008

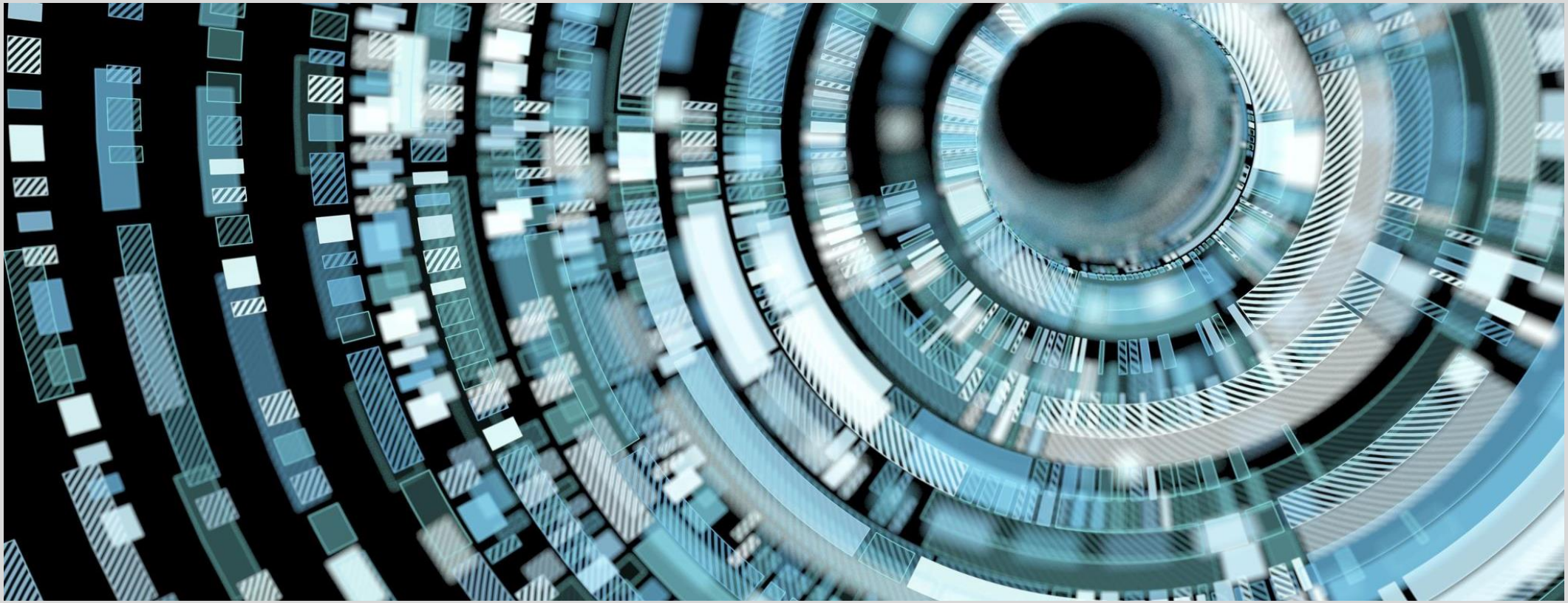
[2]B.T.H. and E.W.T. contributed equally to this work. (received for review July 7, 2008)

Related Article

In This Issue - Nov 04, 2008

Article | Figures & SI | Info & Metrics | PDF

Epigenetic Age



Epigenetic age

- Epigenetic clocks
- Data-driven (machine learning) composite scores
- Methylation on tens or hundreds of CpG loci
- Predictive of either chronological age or morbidity

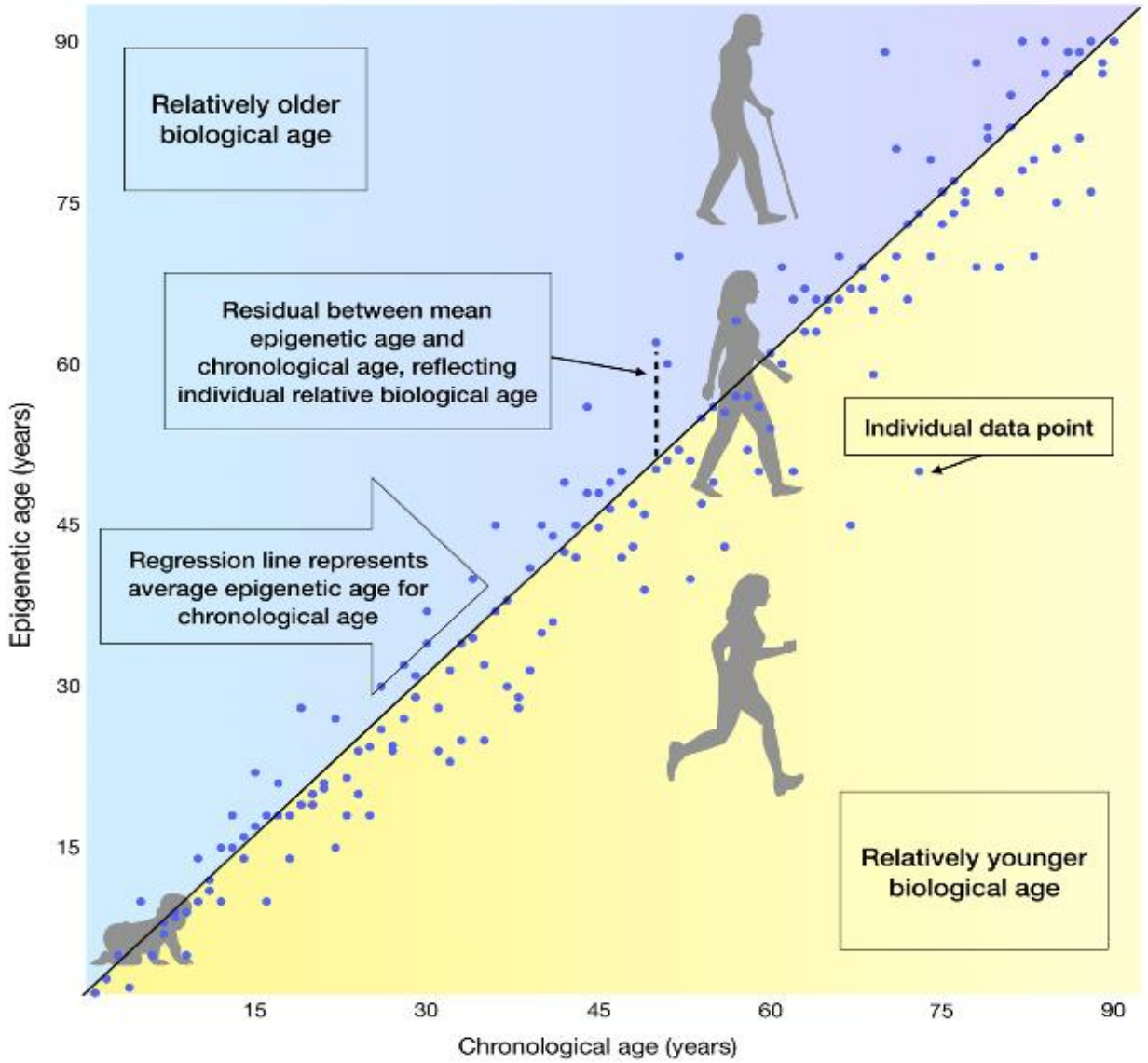
- Chronological vs biological age: individual differences in ageing and disease

Horvath & Raj, 2018

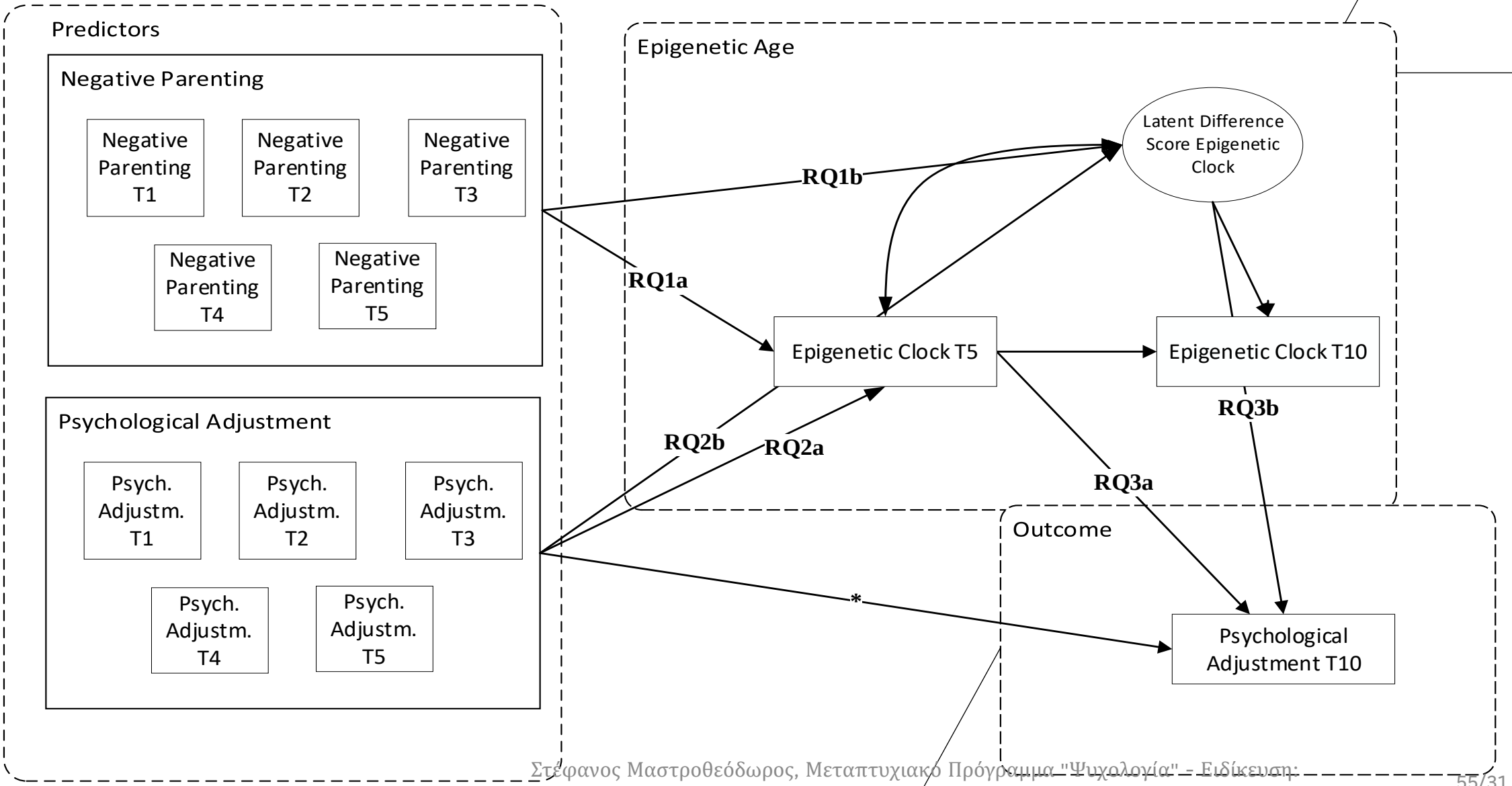
Epigenetic age, stress, and health

- Stress and mental health have been associated with differences between epigenetic age and chronological age

e.g., Guevara & Lawler, 2018; Oblak et al., 2021; Palma-Gudiel et al., 2020; Raffington et al., 2021; Zannas et al., 2015

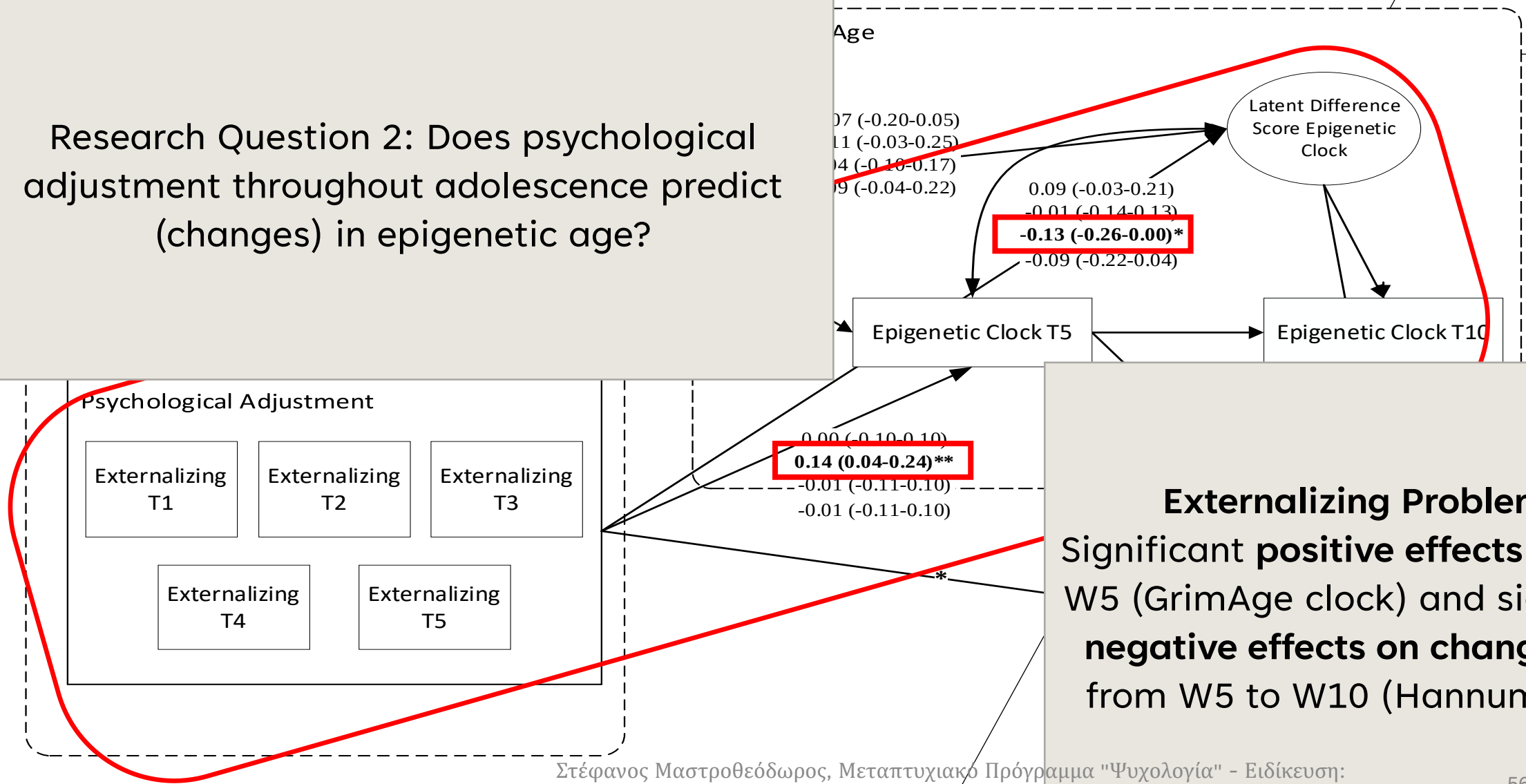


Research Questions



Results – Research Question 2, Externalizing Problems

Research Question 2: Does psychological adjustment throughout adolescence predict (changes) in epigenetic age?

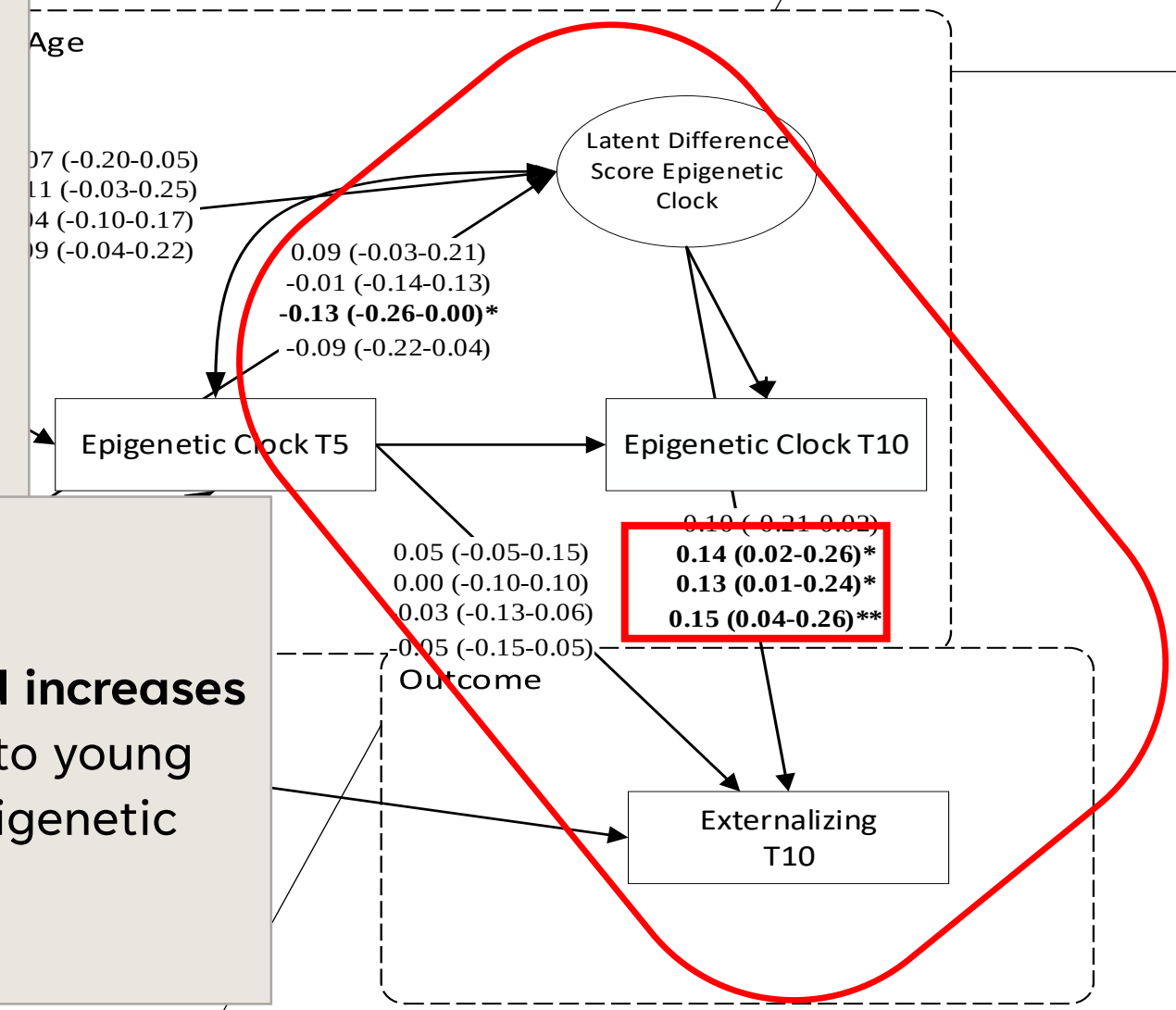


Externalizing Problems:
Significant **positive effects** on EA @ W5 (GrimAge clock) and significant **negative effects on change** in EA from W5 to W10 (Hannum clock)

Results – Research Question 3, Externalizing Problems

Research Question 3: Do changes in epigenetic age predict changes in psychological well-being?

Externalizing Problems:
Changes in EA from age 17 to age 25 **predicted increases in externalizing problems** from adolescence to young adulthood, according to three out of four epigenetic clocks.



Epigenetic Age

Translational Psychiatry

www.nature.com/tp

ARTICLE OPEN

Check for updates

Psychological and biological resilience modulates the effects of stress on epigenetic aging

Zachary M. Harvanek[1], Nia Fogelman[2], Ke Xu[1,3] and Rajita Sinha[1,2,4,5]✉

Epigenetic Age

Translational Psychiatry

www.nature.com/tp

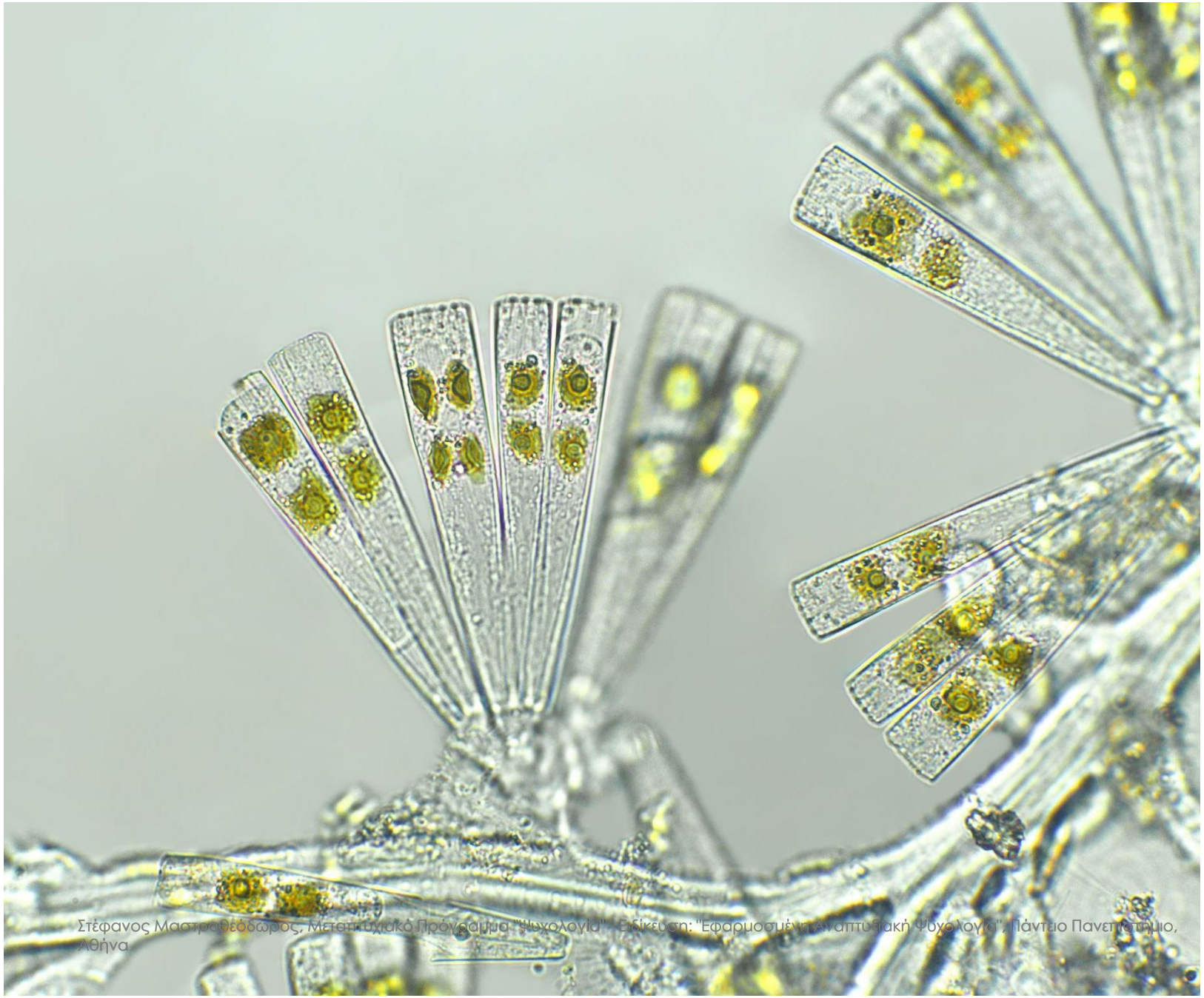
ARTICLE OPEN

Psychological stress on epig

Zachary M. Harvanek[1], Ni

Our society is experiencing more stress than ever before, leading to both negative psychiatric and physical outcomes. Chronic stress is linked to negative long-term health consequences, raising the possibility that stress is related to accelerated aging. In this study, we examine whether resilience factors affect stress-associated biological age acceleration. Recently developed "epigenetic clocks" such as GrimAge have shown utility in predicting biological age and mortality. Here, we assessed the impact of cumulative stress, stress physiology, and resilience on accelerated aging in a community sample ($N = 444$). Cumulative stress was associated with accelerated GrimAge ($P = 0.0388$) and stress-related physiologic measures of adrenal sensitivity (Cortisol/ACTH ratio) and insulin resistance (HOMA). After controlling for demographic and behavioral factors, HOMA correlated with accelerated GrimAge ($P = 0.0186$). Remarkably, psychological resilience factors of emotion regulation and self-control moderated these relationships. Emotion regulation moderated the association between stress and aging ($P = 8.82e{-}4$) such that with worse emotion regulation, there was greater stress-related age acceleration, while stronger emotion regulation prevented any significant effect of stress on GrimAge. Self-control moderated the relationship between stress and insulin resistance ($P = 0.00732$), with high self-control blunting this relationship. In the final model, in those with poor emotion regulation, cumulative stress continued to predict additional GrimAge Acceleration even while accounting for demographic, physiologic, and behavioral covariates. These results demonstrate that cumulative stress is associated with epigenetic aging in a healthy population, and these associations are modified by biobehavioral resilience factors.

Translational Psychiatry (2021)11:601 ; https://doi.org/10.1038/s41398-021-01735-7



Biological substrates of resilience

4th wave in resilience research

- Genetic studies
- Studies on the stress response systems
- Differential sensitivity to experience
- Neurobiological programming and plasticity

Medical influences in resilience research

- Vaccination as a metaphor
- Steeling, inoculation effects
- Hygiene hypothesis
- Developmental timing
- A genetic factor might confer protection against some risk factors, but risk in other respects. E.g., sickle-cell anemia gene.

Stress Inoculation effects → Sense of mastery

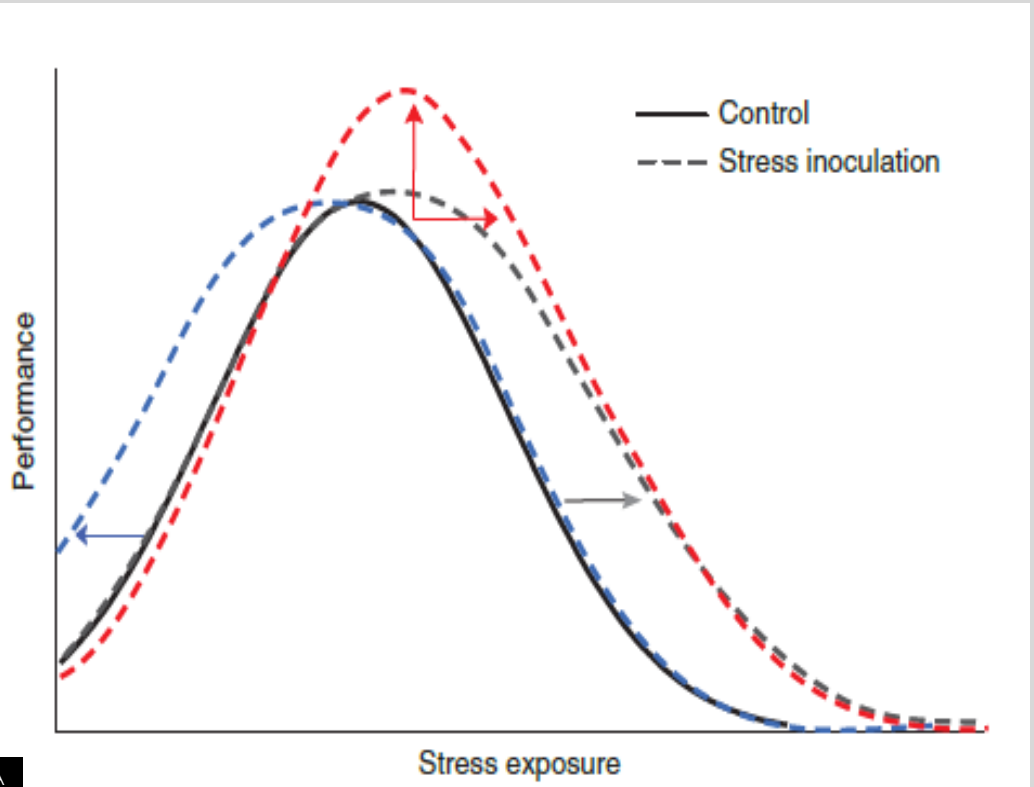
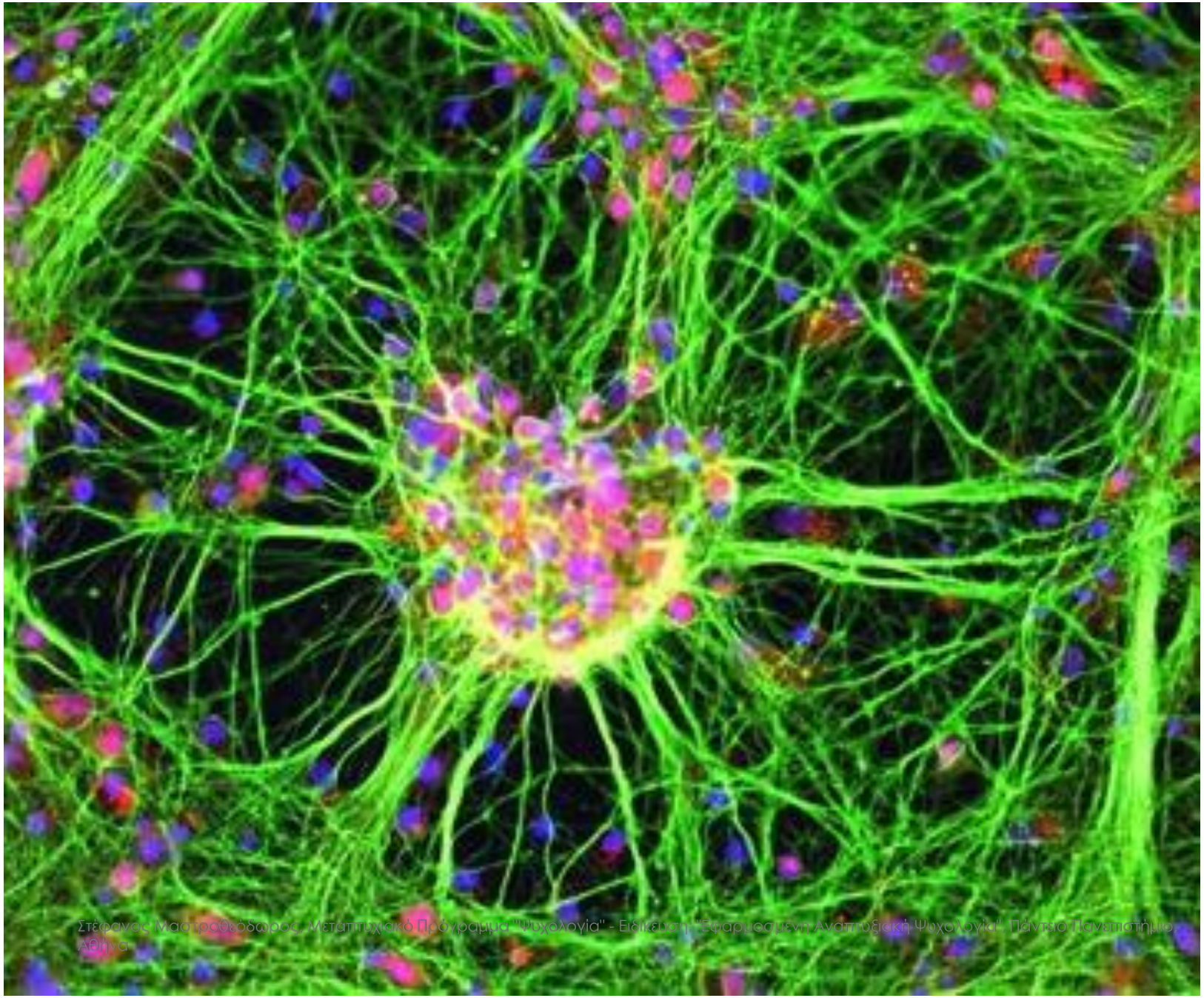
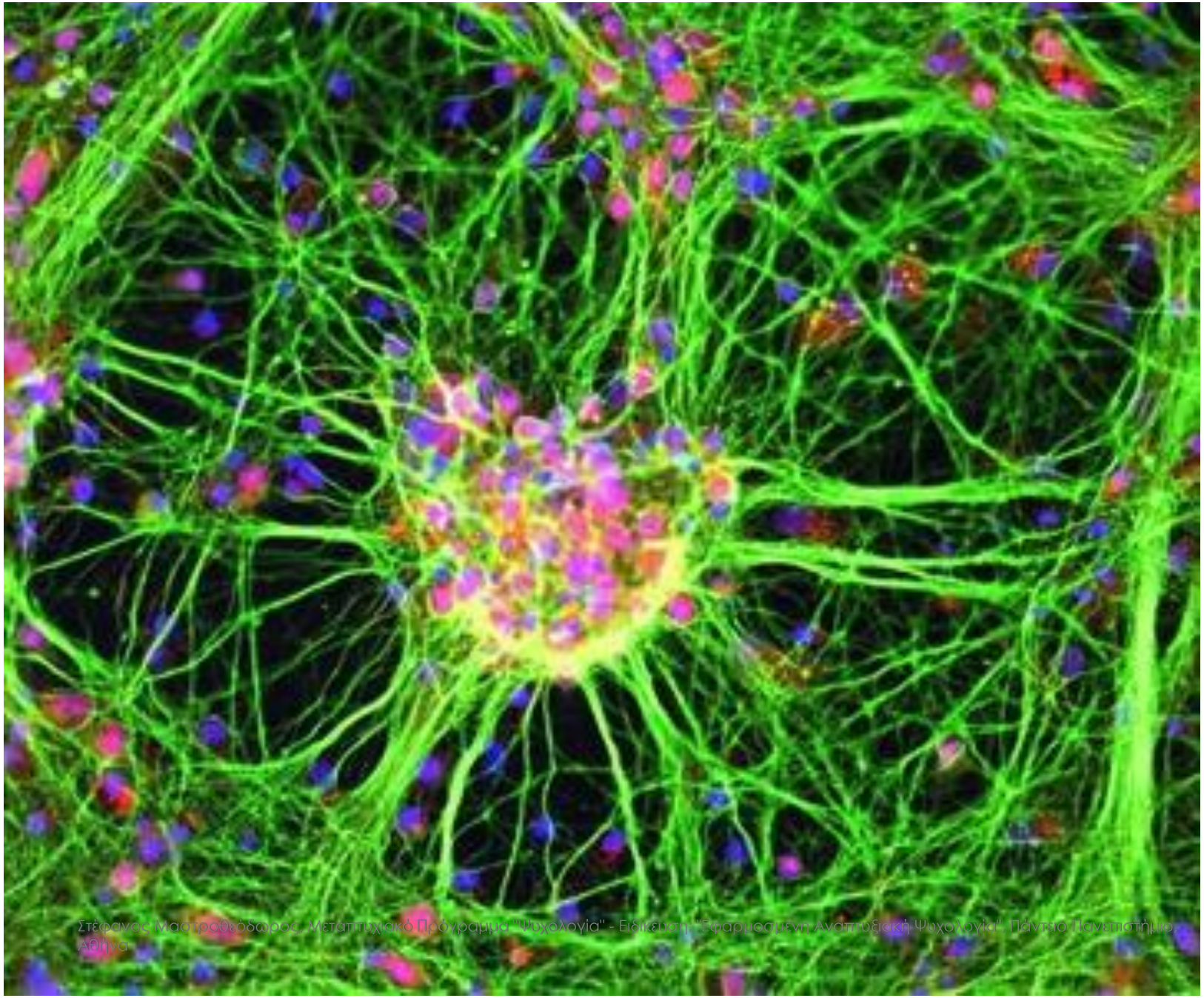


Figure taken from Russo et al., 2012, doi:10.1038/nn.3234



Neurobiological processes

- Early life experiences have a strong effect on the functioning of regulatory systems.
- Rat pup experiments – Quality of parenting
  - High vs low LG mothers
- Specific developmental timing



Neurobiological processes

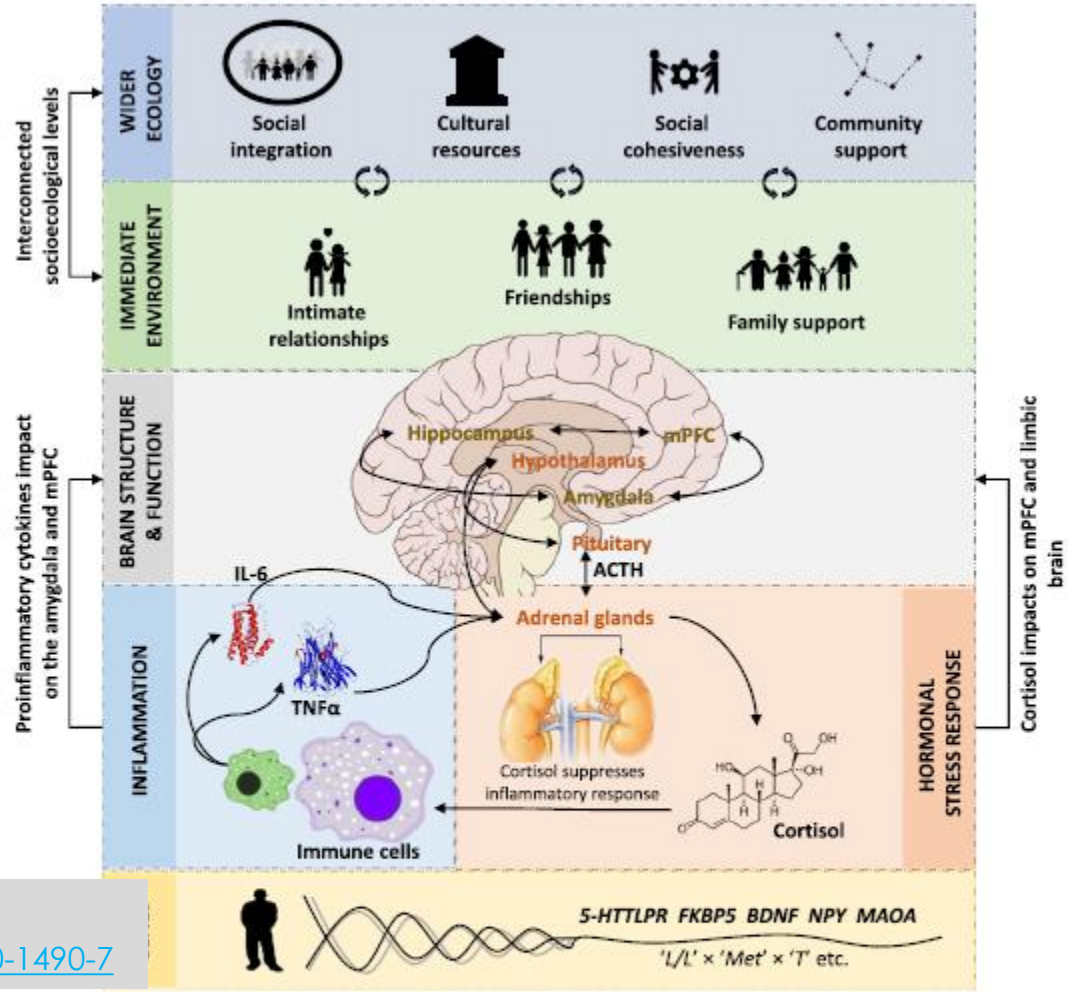
- Problem solving
- Executive functioning (EF) & Self-regulation
  - Hot cognition
- Reward systems

Stress regulation

- Homeostasis and allostatic load
- HPA axis
  - Prolonged activation == hyporesponsive
  - Parenting
- Maternal care: high LG rat mothers → lower gene methylation in HPA axis.

HPA axis

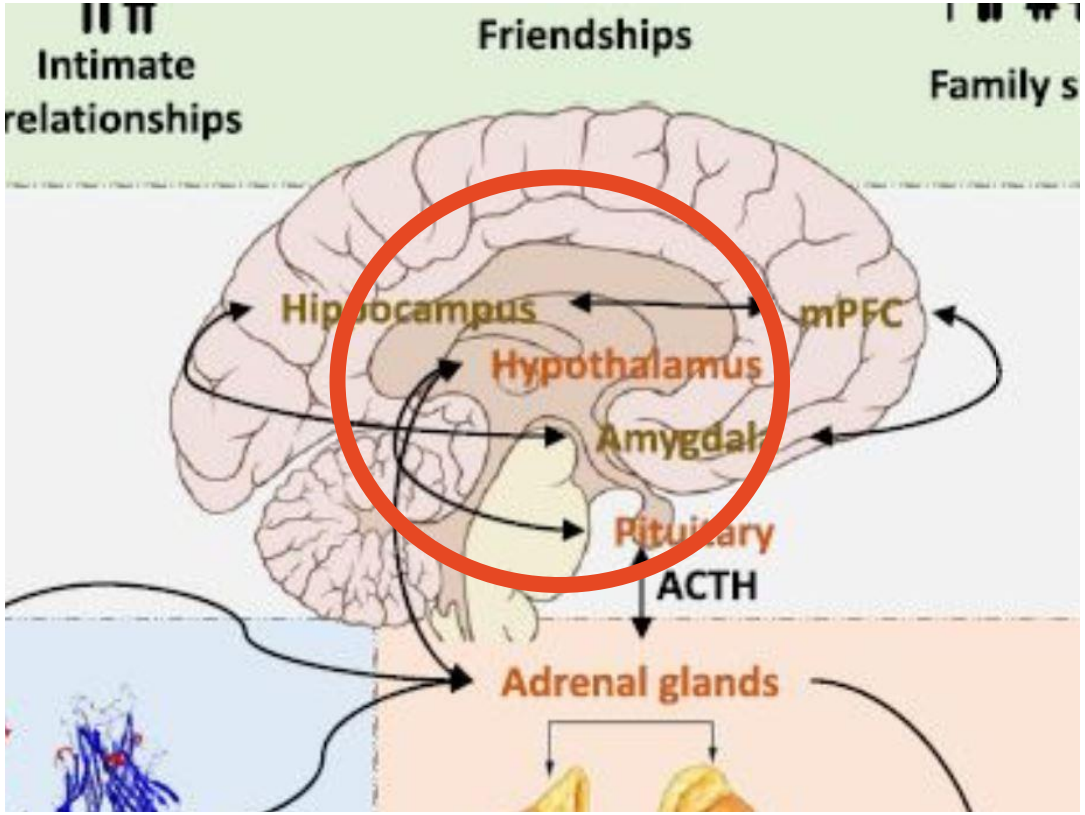
- Hypothalamus-Pituitary-Adrenal axis
- Central role to stress regulation and immune function.
- Stress:
  1. Hypothalamus: release of corticotropin-releasing hormone (CRH)
  2. CRH activates release of adrenocorticotropic hormone (ACTH) from Pituitary
  3. ACTH stimulates release of cortisol from the adrenal cortex.



Ioannidis et al., 2020.
Doi: https://doi.org/10.1186/s12916-020-1490-7

Fig. 2 The complex neurobiology of resilience after childhood maltreatment (CM). Resilient functioning in those individuals who have experienced CM may be facilitated by larger prefrontal cortex (PFC) and hippocampal volume and connectivity, the ability to adequately regulate emotions and dampen stress responsivity, cortisol and proinflammatory baseline and responses, polygenic resilience effects, social support from the immediate environment, and the wider ecology. For readability, the location of the hippocampus is not correct. *5-HTTLPR* serotonin-transporter-linked polymorphic region, *ACTH* adrenocorticotropic hormone; *BDNF* brain-derived neurotrophic factor, *FKBP5* FK binding protein 5, *IL-6* interleukin 6, *MAOA* monoamine oxidase A, *mPFC* medial PFC, *NPY* neuropeptide Y, *TNFα* tumour necrosis factor-α

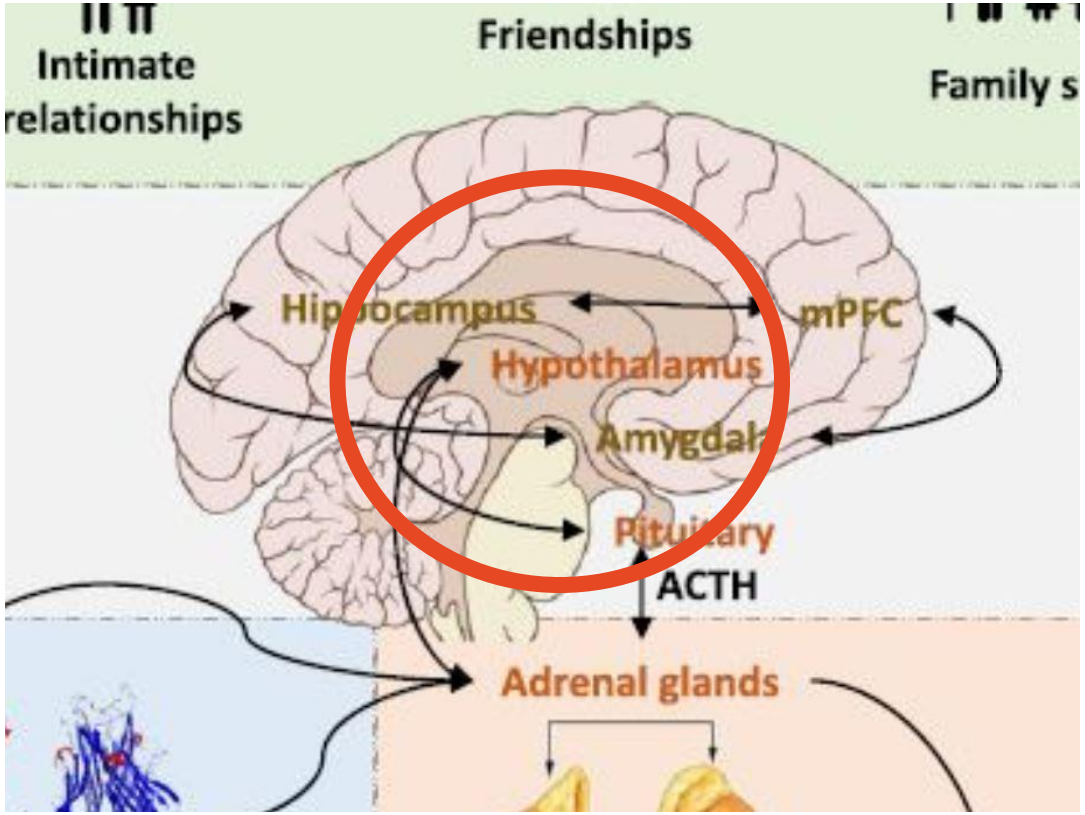
The complex neurobiology of resilient functioning



Ioannidis et al., 2020.
Doi: https://doi.org/10.1186/s12916-020-1490-7

- HPA axis: chronic stress → chronic activation → fatigue and *hypo*-reactivity to stress.
- Feedback loops.
- Epigenetic Processes.
- Mixed results regarding *hyper*- or *hypo*-activation of HPA after child maltreatment.

The complex neurobiology of resilient functioning



Ioannidis et al., 2020.
Doi: https://doi.org/10.1186/s12916-020-1490-7

- Glucocorticoids do have a neurodegenerative effect, but the mechanisms and the cascading consequences are not yet fully understood.
- Effects are dynamic, non-linear, interactive, and multiplicative; not unidirectional, linear, or additive.
- New methods needed: longitudinal designs, multiple time-frames, multi-level measurements.

Original Investigation

FREE

February 2015

Intervention Effects on Diurnal Cortisol Rhythms of Child Protective Services–Referred Infants in Early Childhood

Preschool Follow-up Results of a Randomized Clinical Trial

Kristin Bernard, PhD[1]; Camelia E. Hostinar, PhD[2]; Mary Dozier, PhD[3]

» Author Affiliations | Article Information

JAMA Pediatr. 2015;169(2):112-119. doi:10.1001/jamapediatrics.2014.2369

Interventions positively influence HPA axis in infants

-- experimental intervention

-- Attachment Biobehavioral Catch-up program

-- treatment infants better cortisol response during the day

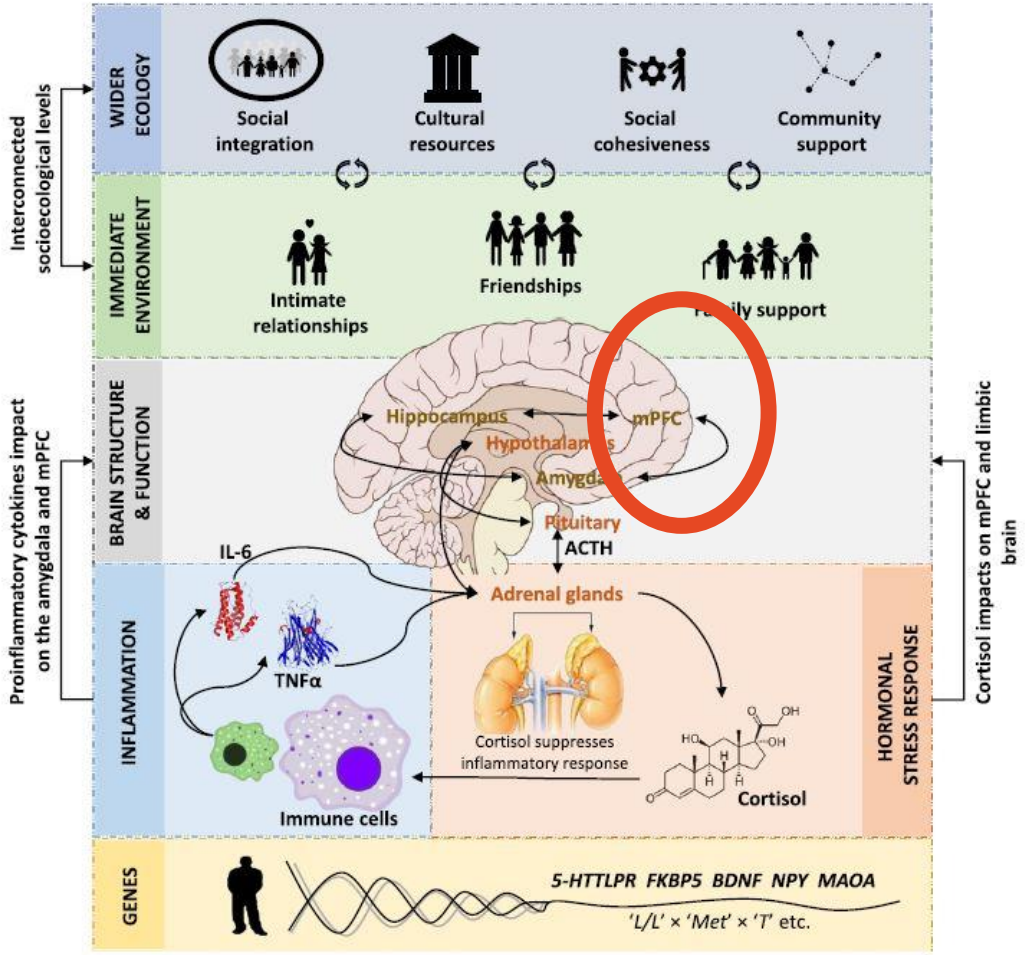
-- differences persisted in 3-month follow-up

Stress response systems

Exposure to stress and HPA functioning: higher methylation on the NR3C1 gene

- McGowan et al., 2009

The complex neurobiology of resilient functioning

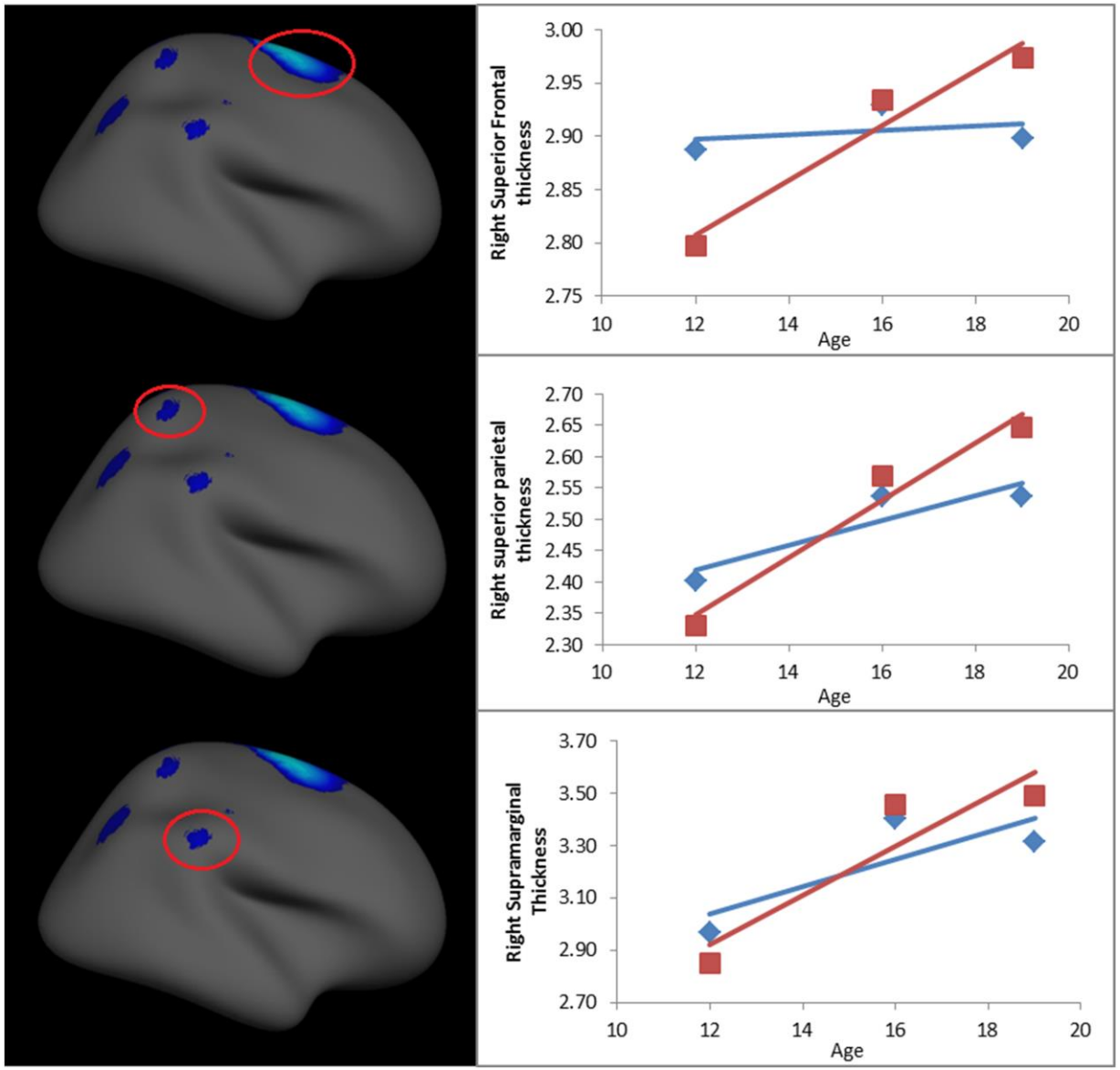


- Prefrontal Cortex (PFC, προμετωπιαίος φλοιός)
- Medial PFC: larger volume in those showing resilient functioning
- Worse functioning: smaller volumes.
- Pre-existing (predisposing) differences, or adaptive, responsive to the environment?
- Possibly PFC → Self-Regulation → Resilient functioning

Example: Observed Measures of Negative Parenting Predict Brain Development during Adolescence (Whittle et al., 2016).

Maternal aggression during early adolescence predicted voluminal increase in certain brain regions for males only.

(red/blue lines: high/low maternal aggression)



OXFORD

Social Cognitive and Affective Neuroscience, 2016, 915–922

doi: 10.1093/scan/nsw025
Advance Access Publication Date: 15 March 2016
Original article

Neural mechanisms linking social status and inflammatory responses to social stress

Keely A. Muscatell,[1,2] Katarina Dedovic,[2,3] George M. Slavich,[4] Michael R. Jarcho,[4,5] Elizabeth C. Breen,[4] Julienne E. Bower,[2,4] Michael R. Irwin,[2,4] and Naomi I. Eisenberger[2]

Muscatell et al., 2016; doi: 10.1093/scan/nsw025

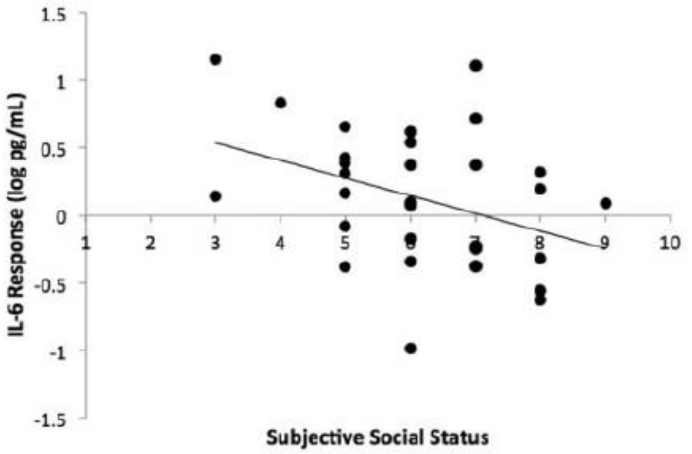


Fig. 1. Lower subjective social status is associated with greater IL-6 responses to the social stressor.

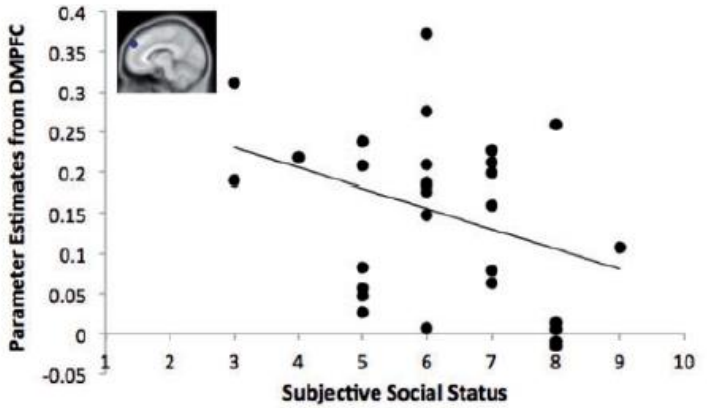


Fig. 2. Lower subjective social status is associated with greater neural activity in the DMPFC ROI in response to negative feedback.

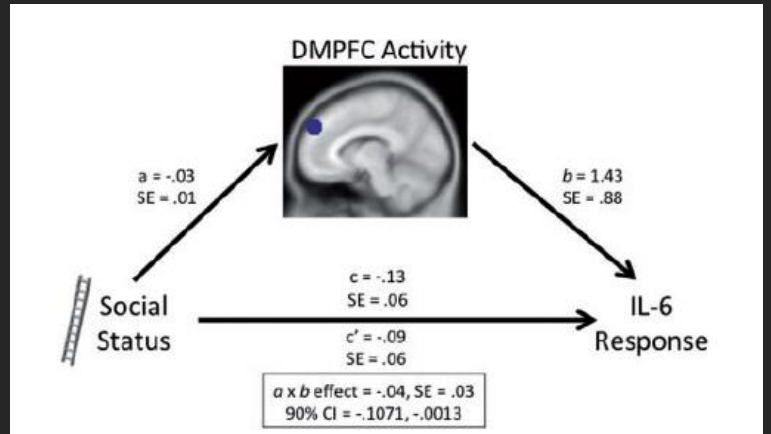
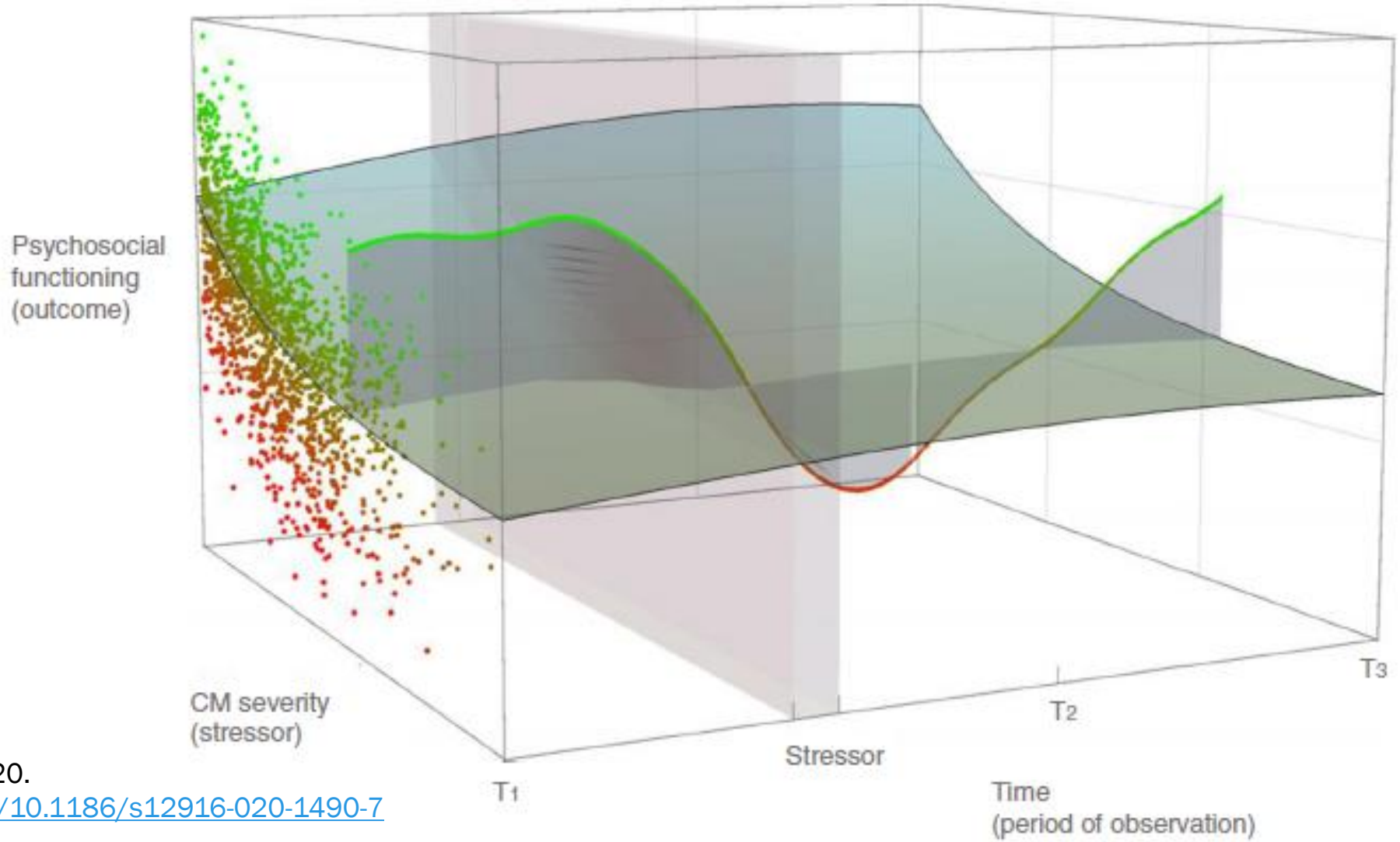


Fig. 3. Mediational model linking subjective social status and inflammatory responses via activation in the DMPFC.
Note: *a*, *b*, *c* and *c'* refer to the unstandardized coefficients for each path in the model; SE refers to the standard error for each effect.



Ioannidis et al., 2020.
Doi: https://doi.org/10.1186/s12916-020-1490-7

Fig. 3 Trajectory of a complex resilience system in phase space. Resilience hyperplane plot of simulated data of childhood maltreatment (CM) severity (x-axis: stressor variable), psychosocial functioning (y-axis: outcome variable) and time (z-axis: period of observation), created by fitting a polynomial regression surface determined by numerical predictors of x, y and z using local fitting. An individual trajectory was hypothesised to demonstrate a complex system trajectory above and below the regression plane. Data points above the hyperplane (green) characterise 'resilient functioning', whereas all data points below the hyperplane (red) characterise non-resilient functioning at any time point (cross-sectionally)

The complex neurobiology of resilience – The immune system

- Stress energizes proinflammatory responses releasing agents (e.g., interleukin 6, tumour necrosis factor-a), which energize the HPA to release corticosteroids, which stop the immune reaction.
  - Chronic stress results in cortisol resistance, reducing the capacity of cortisol to stop the immune reaction → inflammation.
- Animal models: low inflammation factors were associated with resilience against stress in mice.
- The effects of social support on psychosocial adjustment after maltreatment might be mediated by neurobiological mechanisms.

Promising Future directions: Exposome

Exposome

www.humanexposomeproject.com

“You are more than your genes. The exposome captures the non-genetic influences on health and disease.”

Exposome

https://www.humanexposome.eu/

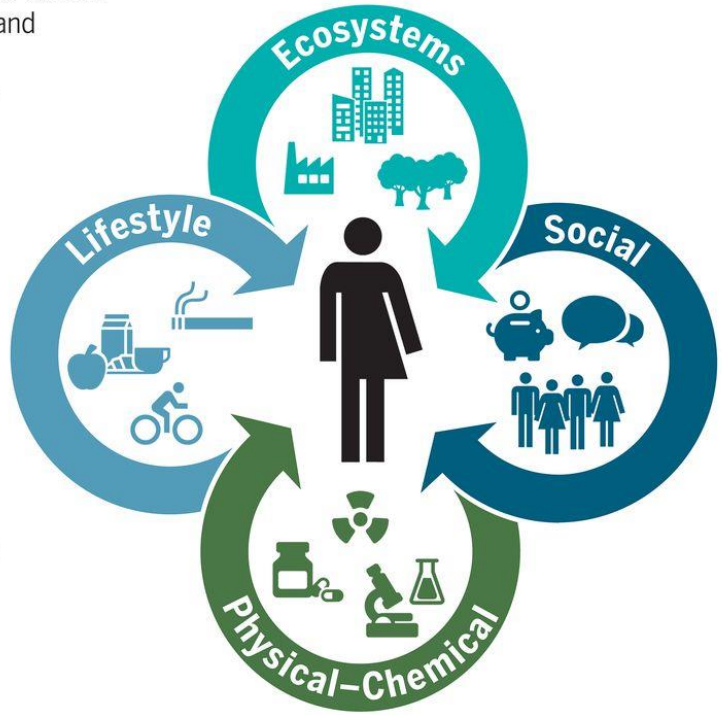
The human exposome encompasses exposures to environmental factors **throughout life**, starting from conception and pregnancy.

Exposome

Ecosystems
Food outlets, alcohol outlets
Built environment and urban land uses
Population density
Walkability
Green/blue space

Lifestyle
Physical activity
Sleep behavior
Diet
Drug use
Smoking
Alcohol use

Social
Household income
Inequality
Social capital
Social networks
Cultural norms
Cultural capital
Psychological and mental stress



Physical–Chemical
Temperature/humidity
Electromagnetic fields
Ambient light
Odor and noise
Point, line sources, e.g, factories, ports
Outdoor and indoor air pollution
Agricultural activities, livestock
Pollen/mold/fungus
Pesticides
Fragrance products
Flame retardants (PBDEs)
Persistent organic pollutants
Plastic and plasticizers
Food contaminants
Soil contaminants
Drinking water contamination
Groundwater contamination
Surface water contamination
Occupational exposures

Taken from: Vermeulen, Schymanski, Barabási, & Miller, 2020. The exposome and health: Where chemistry meets biology. *Science*, 367(6476). DOI: 10.1126/science.aay3164

Σύνοψη

- Η ψυχική ανθεκτικότητα μπορεί να διαπιστωθεί υπό συνθήκες, δεν μετριέται γενικά.
- Η ψυχική ανθεκτικότητα είναι εξ ορισμού μια δυναμική διεργασία, που εξελίσσεται στον χρόνο.
- Ο τύπος και η χρονική συγκυρία των παραγόντων κινδύνου επηρεάζει την πιθανότητα ψυχικά ανθεκτικής προσαρμογής.
- Ειδικά οι νευροβιολογικές βάσεις και αντιδράσεις που εμπλέκονται στην ψυχική ανθεκτικότητα εξαρτώνται από τη συγκυρία και τον τύπο παραγόντων κινδύνου.
- Διαφορετικά κέντρα του ΚΝΣ έχουν διαφορετικές ευαίσθητες περιόδους.

Σας ευχαριστώ για την προσοχή σας!

Στέφανος Μαστροθεόδωρος, Μεταπτυχιακό Πρόγραμμα "Ψυχολογία" - Ειδίκευση: "Εφαρμοσμένη Αναπτυξιακή Ψυχολογία", Πάντειο Πανεπιστήμιο, Αθήνα

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Στα Άγραφα ...