Global Epigenetics

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Global Epigenetics

Modelling emergence of transgenerational schizophrenia

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a CSSS 2018 project

Introduction

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The New York Review of Books

Epigenetics: The Evolution Revolution

Israel Rosenfield and Edward Ziff
JUNE 7, 2018 ISSUE

At the end of the eighteenth century, the French naturalist Jean-Baptiste Lamarck noted that life on earth had evolved over long periods of time into a striking variety of organisms. He sought to explain how they had become more and more complex. Living organisms not only evolved, Lamarck argued; they did so very slowly, "little by little and successively." In Lamarckian theory, animals became more diverse as each creature strove toward its own "perfection," hence the enormous variety of living things on earth. Man is the most complex life form, therefore the most perfect, and is even now evolving.

Cav O

Children in Amsterdam during the Dutc 1945

In Lamarck's view, the evolution of life depends on variation and the accumulation of small, gradual changes. These are also

Soc Psychiatry Psychiatr Epidemiol (1998) 33: 373–379

ORIGINAL PAPER

H.W. Hoek · A.S. Brown · E. Susser

The Dutch Famine and schizophrenia spectrum dis

Accepted: 11 February 1998

Abstract In the Dutch Hunger Winter at the end of World War II a combination of circumstances created the conditions of a natural experiment. Unlike other famines, the Dutch famine struck at a precisely circumscribed time and place, and in a society able to document the timing and severity of the nutritional deprivation as well as the effects on fertility and health. Because the Dutch maintained comprehensive military and health records, it was possible to compare the incidence of neurodevelopmental disorders in adulthood for birth cohorts exposed versus those unexposed to prenatal famine. We have conducted several studies guided by the hypothesis that prenatal micronutrient deficiencies can cause neurodevelopmental schizophrenia or related personality disorders. In this paper we shall summarize our previous work and combine the outcome data of the different studies. Early prenatal famine was found to be specifically and robustly associated with each of three conditions: (1) congenital anomalies of the central nervous system, (2) schizophrenia, and

Introduction

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Developments in
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OPEN

Citation: Transl Psychiatry (2016) 6, e837; doi:10.1038/tp.2016.109
www.nature.com/tp

ORIGINAL ARTICLE

Elevated paternal glucocorticoid ex noncoding RNA profile in sperm a depressive phenotypes in the offspr

AK Short[1], KA Fennell[1,2], VM Perreau[1], A Fox[1], MK O'Bryan[3], JH Kim[1], TW E

Recent studies have suggested that physiological and behavioral traits m
lineage, possibly via non-genomic signals derived from the sperm. To in
behavioral phenotypes, a model of hypothalamic–pituitary–adrenal (HPA
administered water supplemented with corticosterone (CORT) for 4 weeks
not male; F1 offspring of CORT-treated fathers displayed altered fear extin
altered patterns of ultrasonic vocalization at postnatal day 3 and, as adult
maze and time in light on the light–dark apparatus, suggesting a hypera
treatment. Interestingly, expression of the paternally imprinted gene *Igf2*
but downregulated in female offspring. Male and female F2 offspring dis
elevated-plus maze, suggesting lower levels of anxiety compared with co
immobility time on the forced-swim test and increased latency to feed o
depression-like phenotype in these animals. Collectively, these data provi
and depression-related behaviors across multiple generations. Analysis of
revealed marked effects on the expression of small noncoding RNAs. Sper
three microRNAs, miR-98, miR-144 and miR-190b, which are predicted to
Bdnf. Sustained elevation of glucocorticoids is therefore involved in the t
generations in a process involving small noncoding RNA signals transmit

Translational Psychiatry (2016) **6**, e837; doi:10.1038/tp.2016.109; publishe

INTRODUCTION

There is now growing preclinical and epidemiological evidence supporting a transgenerational influence of paternal stress on the behavior of offspring in a manner not involving direct parenting

mice
behav
induci
viral

Epigenetic selection and the DNA methylation signatures of adverse prenatal environments

Selection as an explanation for epigenetic patterns associated with early prenatal adversity

Elmar W Tobi[1,2,*], Joost van den Heuvel[3,4*], Bas J. Zwaan[4], L.H. Lumey[1,5] Bastiaan T. Heijmans[1,&,&] & Tobias Uller[6,7,&,&]

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7. Department of Biology, University of Lund, Sölvegatan 37, 22362 Lund, Sweden

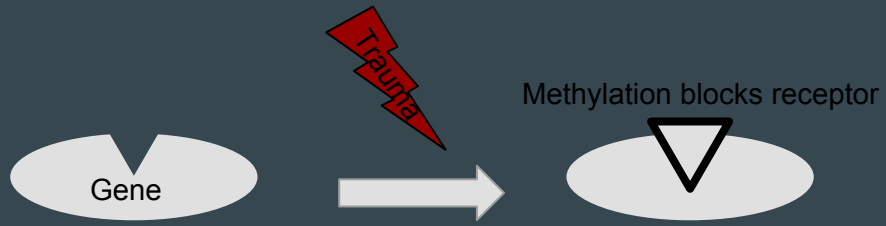
*Joint first author

Epigenetics and mental health

‘Nongenetic influences on gene expression’

Trauma can lead to:

- Methylation: epigenetic modification on the Glucocorticoid receptor gene
- Blocked receptor cannot regulate cortisol effectively
- Cortisol runs up like temperature due to broken thermostat
- Chronic stress linked to worse mental health outcomes



Epigenetics and mental health

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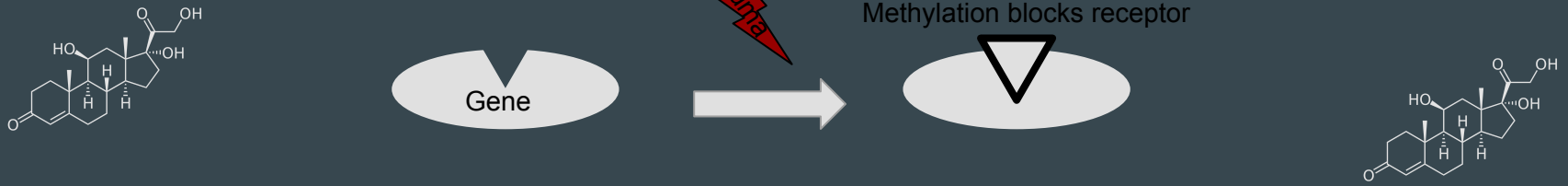
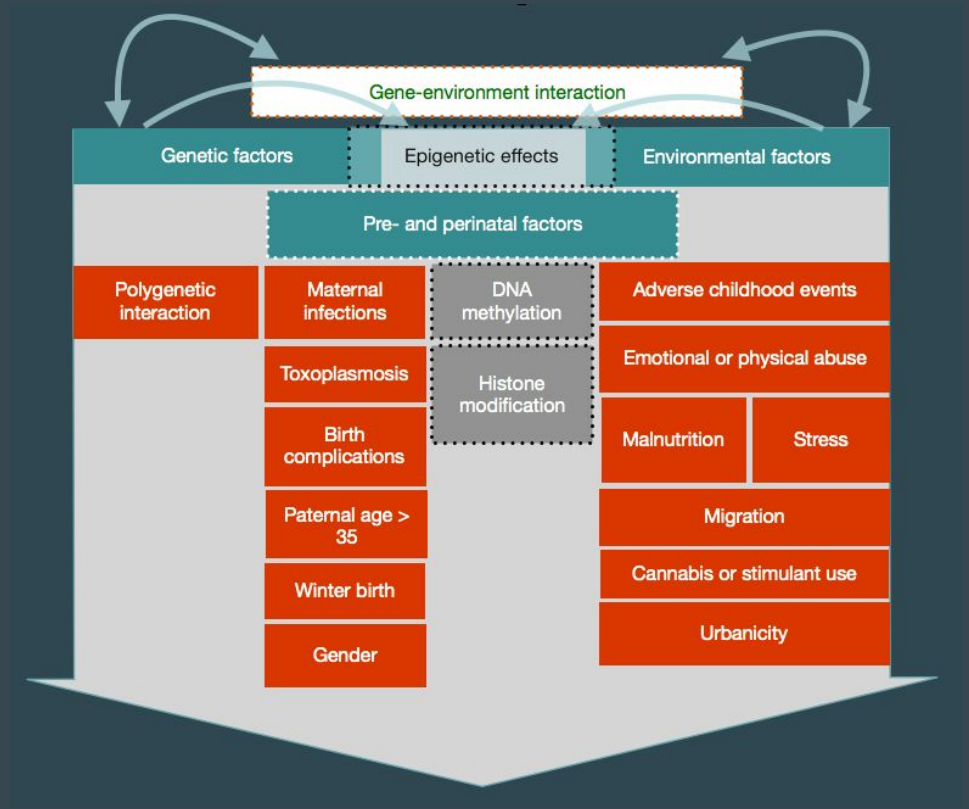


Dutch Hunger Winter (1944–1945)

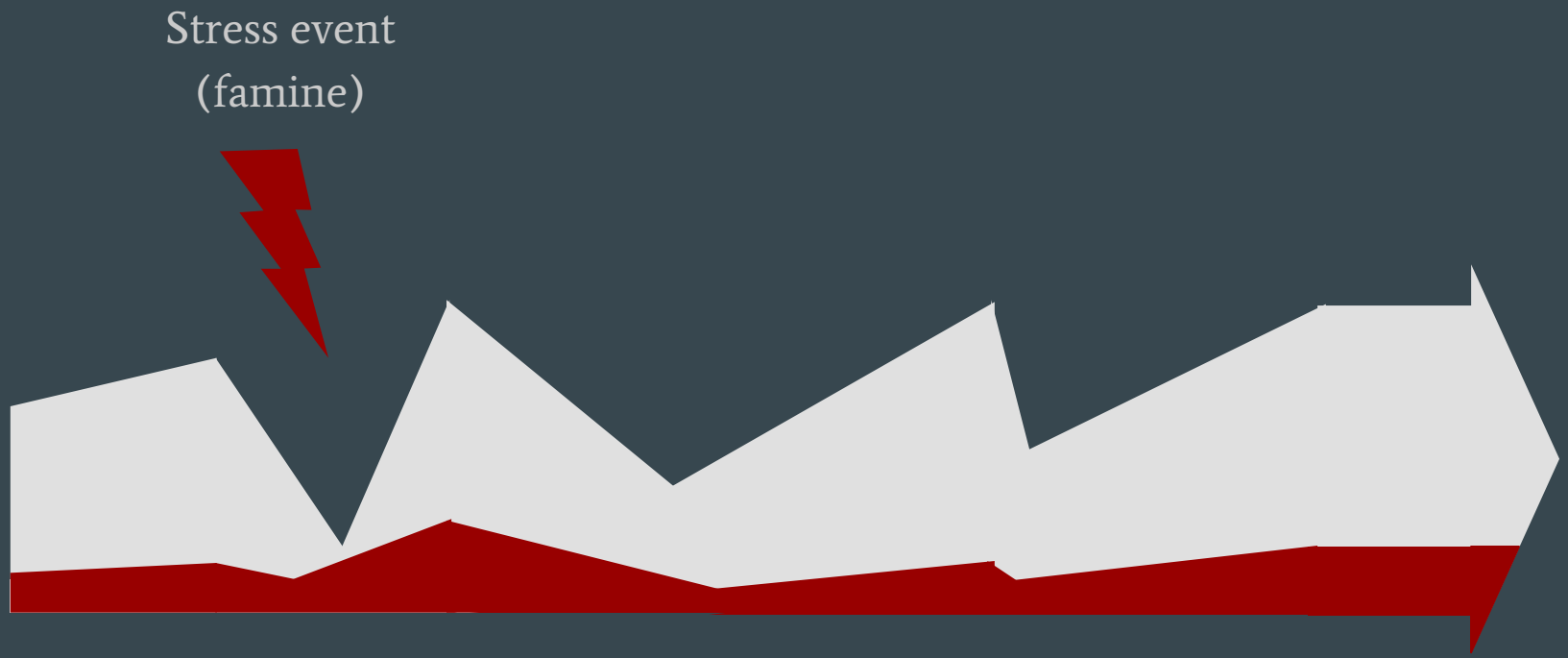
- Famine in Western provinces of the Netherlands during WWII
- Adult food rations dropper under 1000 cal/day in 1944, and further to 580 cal/day in 1945
- In children of mothers *on the third trimester* during famine: Increased risk ratio for schizophrenia twofold
- Similar results for schizophrenia following the Chinese Famine of 1959–1961

Hejmans et al., 2008; Lumey et al. 2009; St Clair et al., 2005; Veenendaal et al., 2013

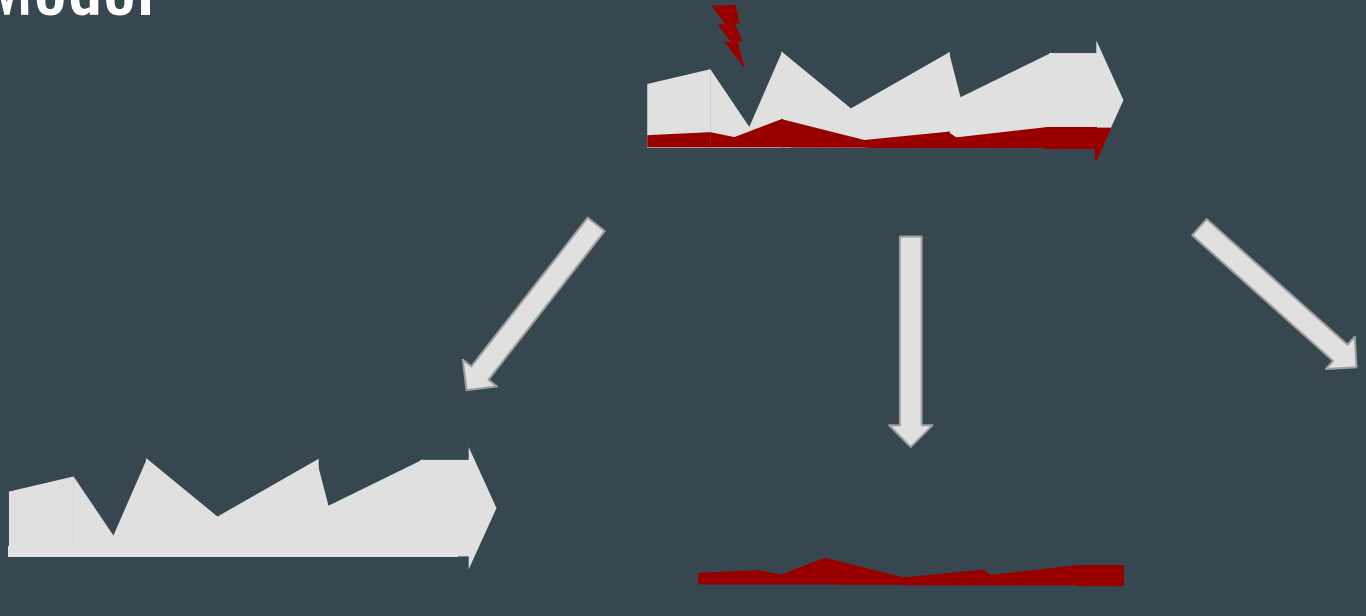
Aetiology of Schizophrenia (a simplified model)



Model



Model



Demographic model

Netherland census data (fertility, mortality)

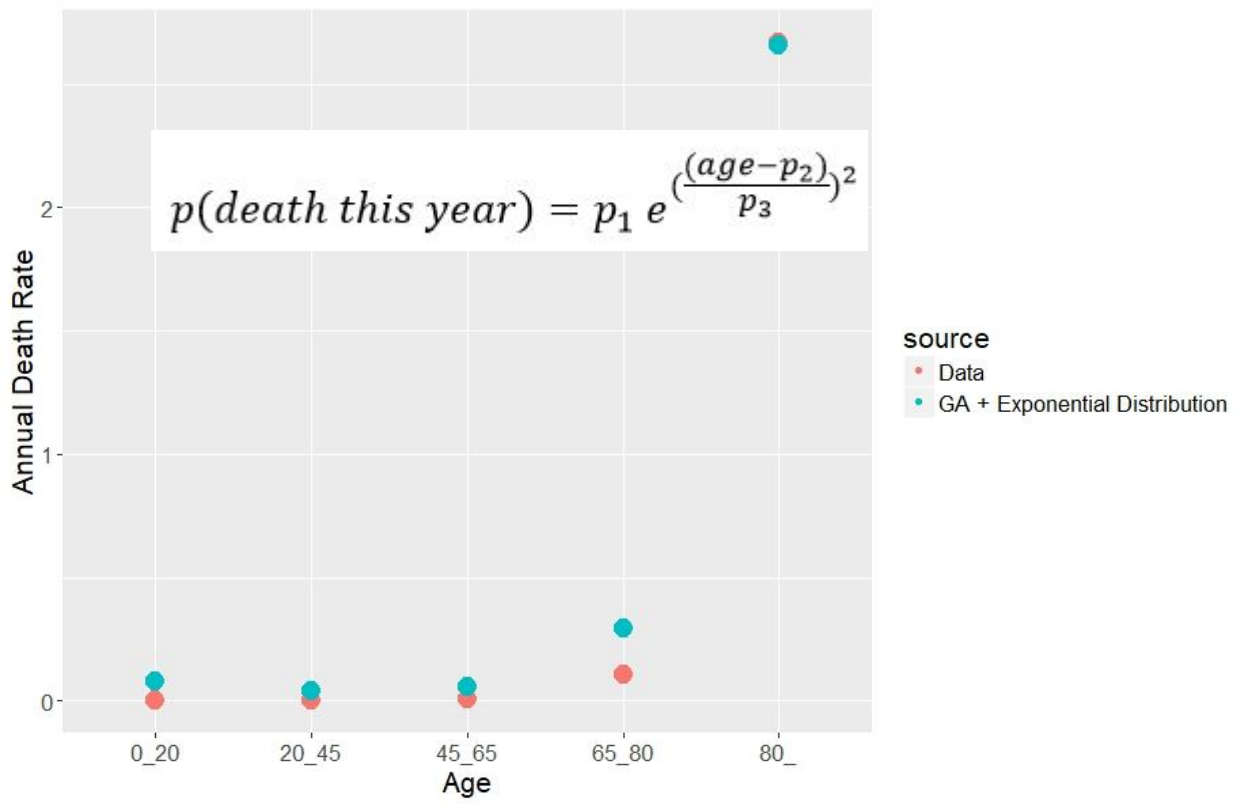
Heritability model

Review of schizophrenia heritability studies

Environmental effect

Dutch famine cohort data

Genetic Algorithm to Fit Exponential Model of Mortality Rates



Fitting Exponential Mortality Model With Regression

lm(formula = probDeath.1940 ~ exp(ageGroup.1940))

Coefficients:

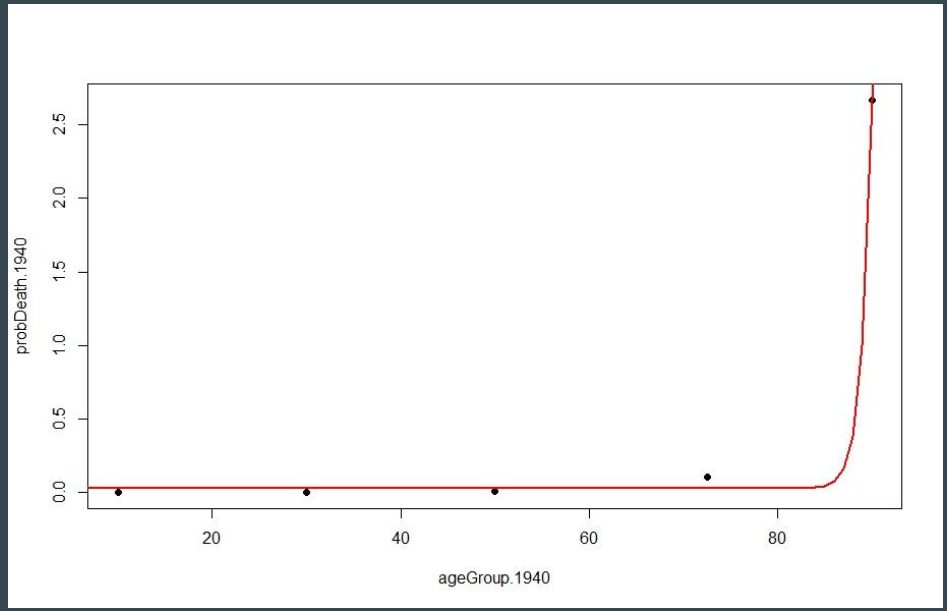
	Estimate	Std. Error	t value	Pr(>|t|)	
(Intercept)	2.912e-03	2.134e-03	1.364	0.30571	
exp(ageGroup.1940)	3.344e-33	1.393e-34	24.009	0.00173	**

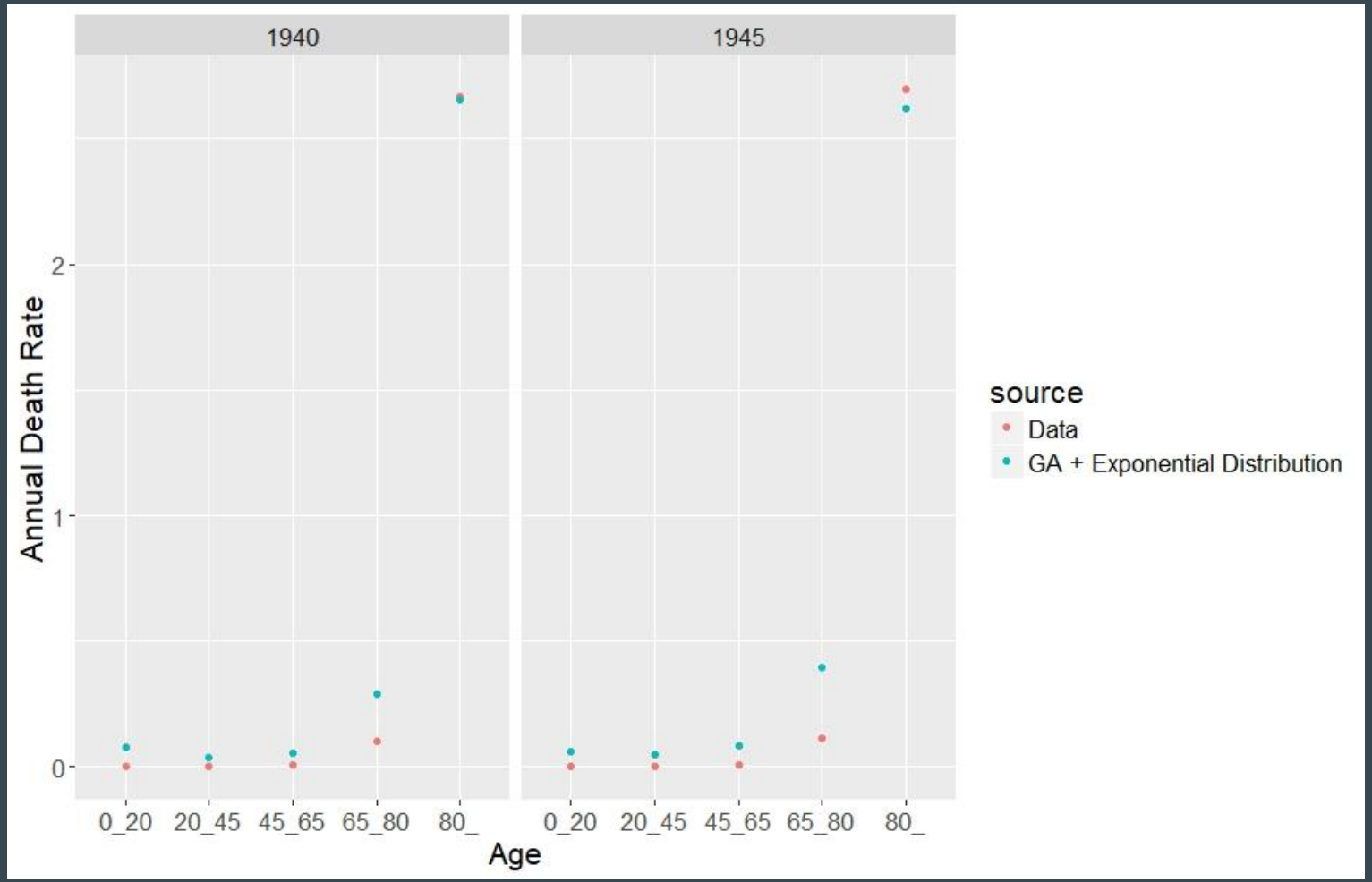
Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

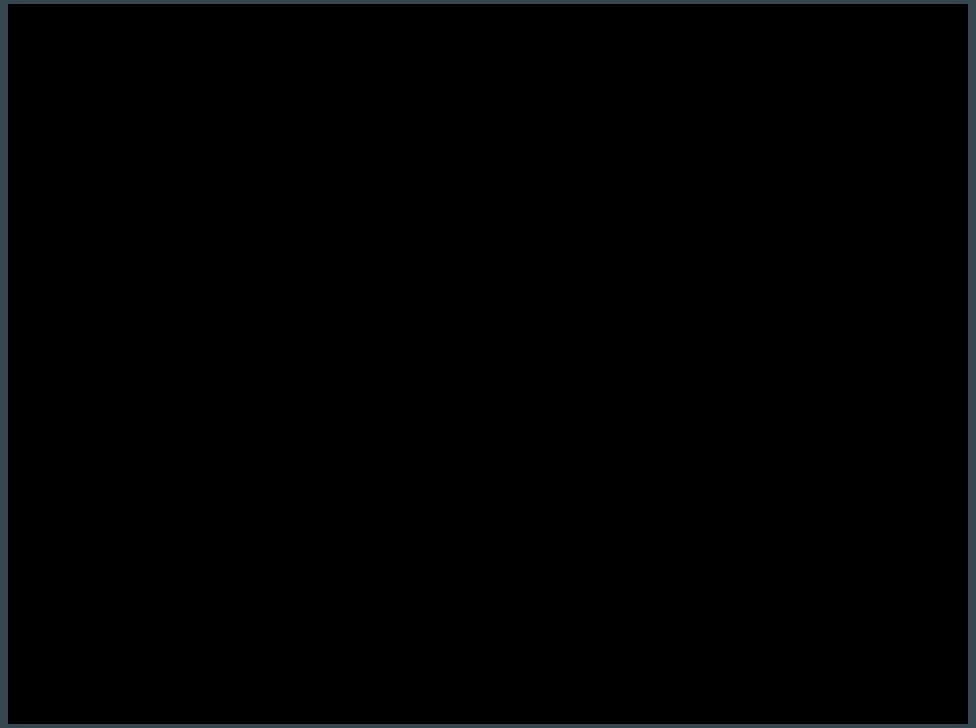
Residual standard error: 0.003697 on 2 degrees of freedom

Multiple R-squared: 0.9965, Adjusted R-squared: 0.9948

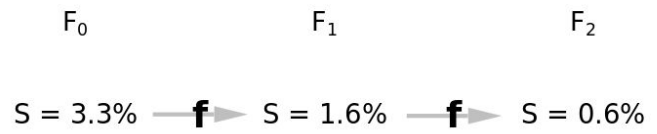
F-statistic: 576.4 on 1 and 2 DF, p-value: 0.00173



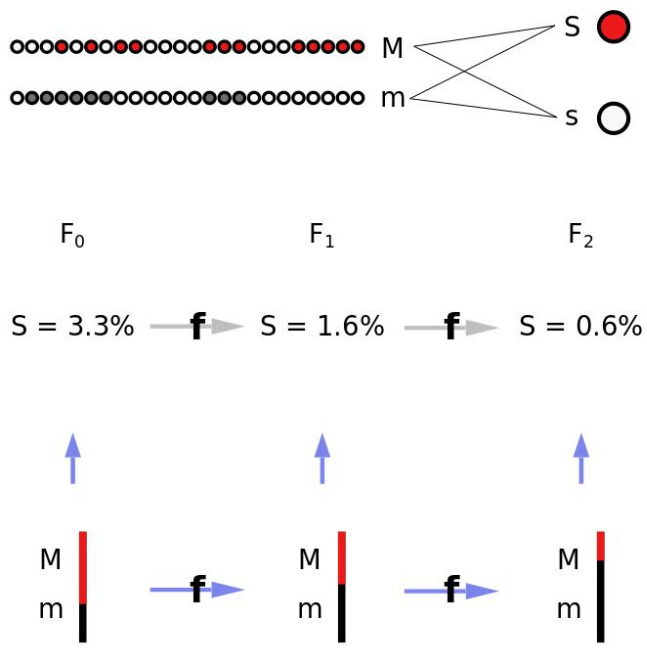

1940
1945
Annual Death Rate
2
1
0
0_20
20_45
45_65
65_80
80_
Age
source
Data
GA + Exponential Distribution

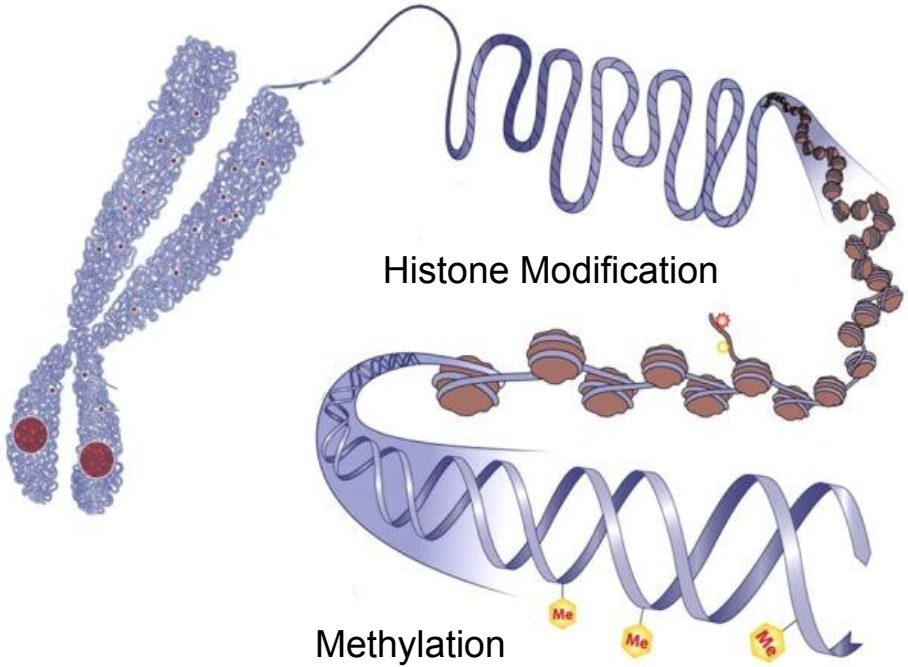


Epigenetic mechanism



Epigenetic mechanism





Future direction

- Improve the calibration of the demographic model
- Stress scenarios on schizophrenia prevalence
- Cost return of interventions
- Run modelling on real-world issues:
  - Early childhood trauma associated with Trump immigration policy
  - Refugee migration
  - Future mental health impacts of large-scale civil crisis such as Syria

- When data is available - expand model to other mental health issues; anxiety, depression.

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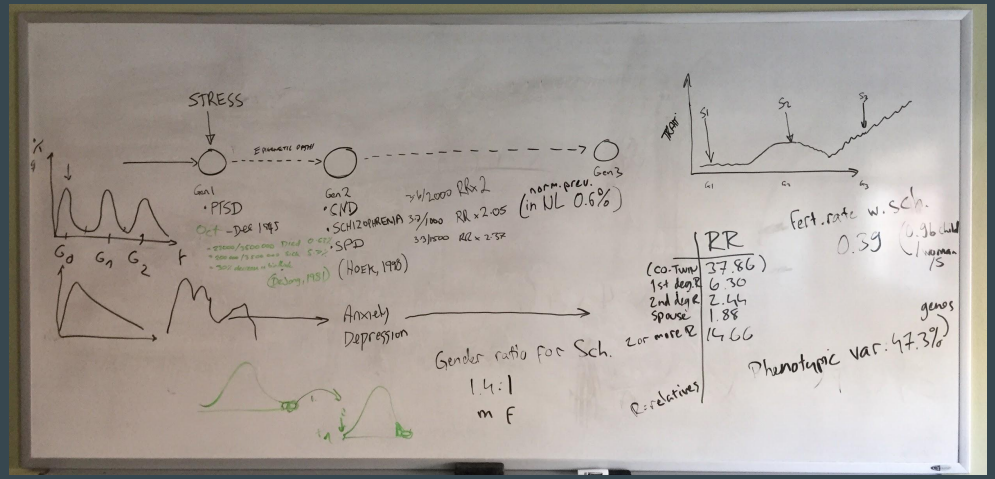
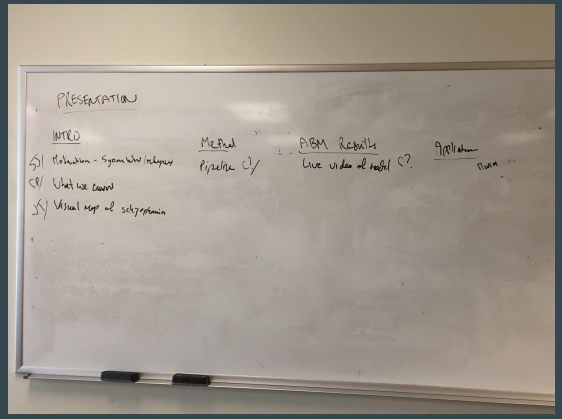
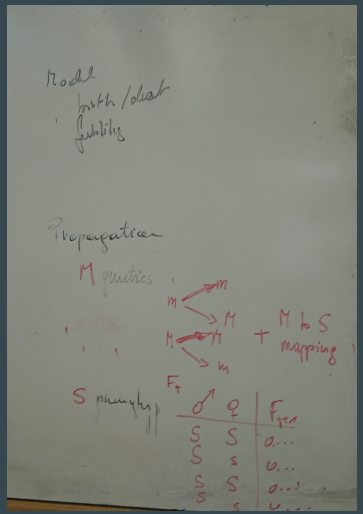
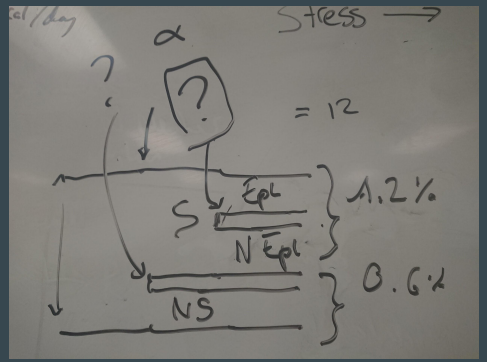

STRESS
Epigenetic path
Gen1
• PTSD
Gen2
• CND
• SCHIZOPHRENIA
• SPD
Gen3
(HOEK, 1998)
Anxiety
Depression
Gender ratio for Sch.
1.4:1
m F
RR
(co-Twin) 37.86
1st deg R 6.30
2nd deg R 2.46
Sparse 1.88
2 or more R 14.66
R: relatives
Fert. rate w.sch.
0.39
genos
Phenotypic var. 47.3%


PRESENTATION
Method
Pipeline
Live video of testing


Model
birth/about
Propagation
Mutations
M to S
mapping
S phenotype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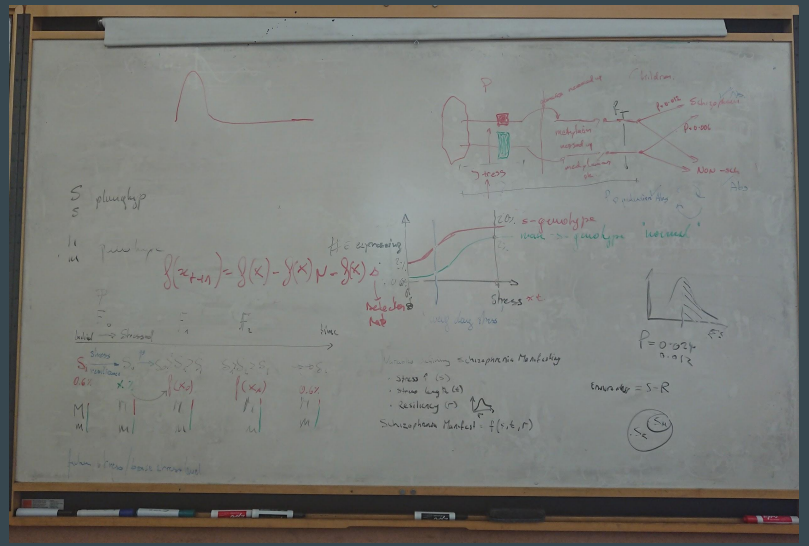
N Epi
NS
11.2%
0.6%


S phenotype
Stress
Time