

Trauma-related genetic,
epigenetic and molecular
factors contributing to
mental illness – what do
we know?

Dr Natalie Matosin
NHMRC Research Fellow (CJ Martin)

Illawarra Health and Medical Research Institute
Molecular Horizons
School of Chemistry and Molecular Bioscience
University of Wollongong
Translational Research In Psychiatry
Max Planck Institute of Psychiatry

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Overview

1. Molecular mechanisms of stress
2. Overview of refugee biology research
3. Our project - TRIP



1. Molecular mechanisms of stress



I am a molecular neuroscientist who specialises in how stress contributes to the development of mental illness



Refugees are extremely stress exposed people who are at risk for developing severe psychiatric issues.



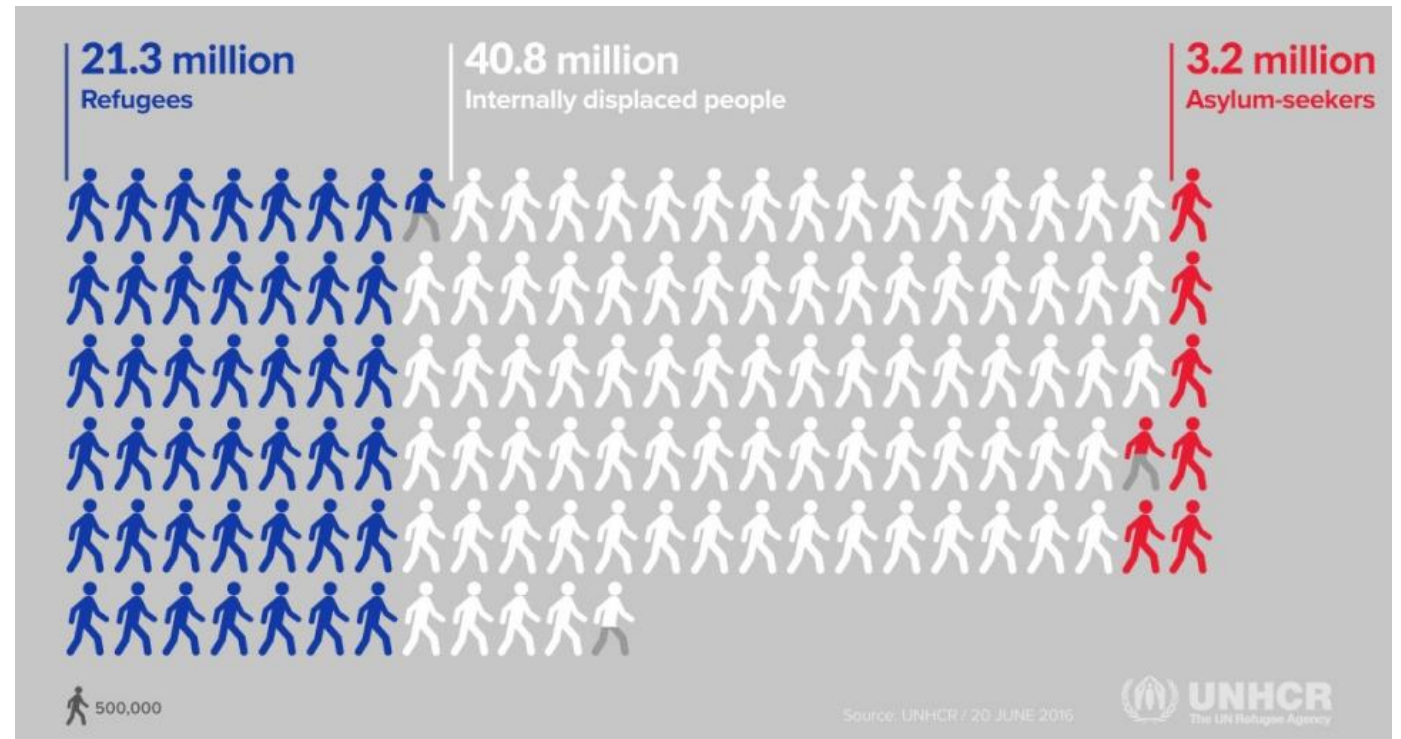
I witnessed first-hand the impact that mass migration has on a host country, and I was moved to use my skillset as a stress scientist to do something about it.



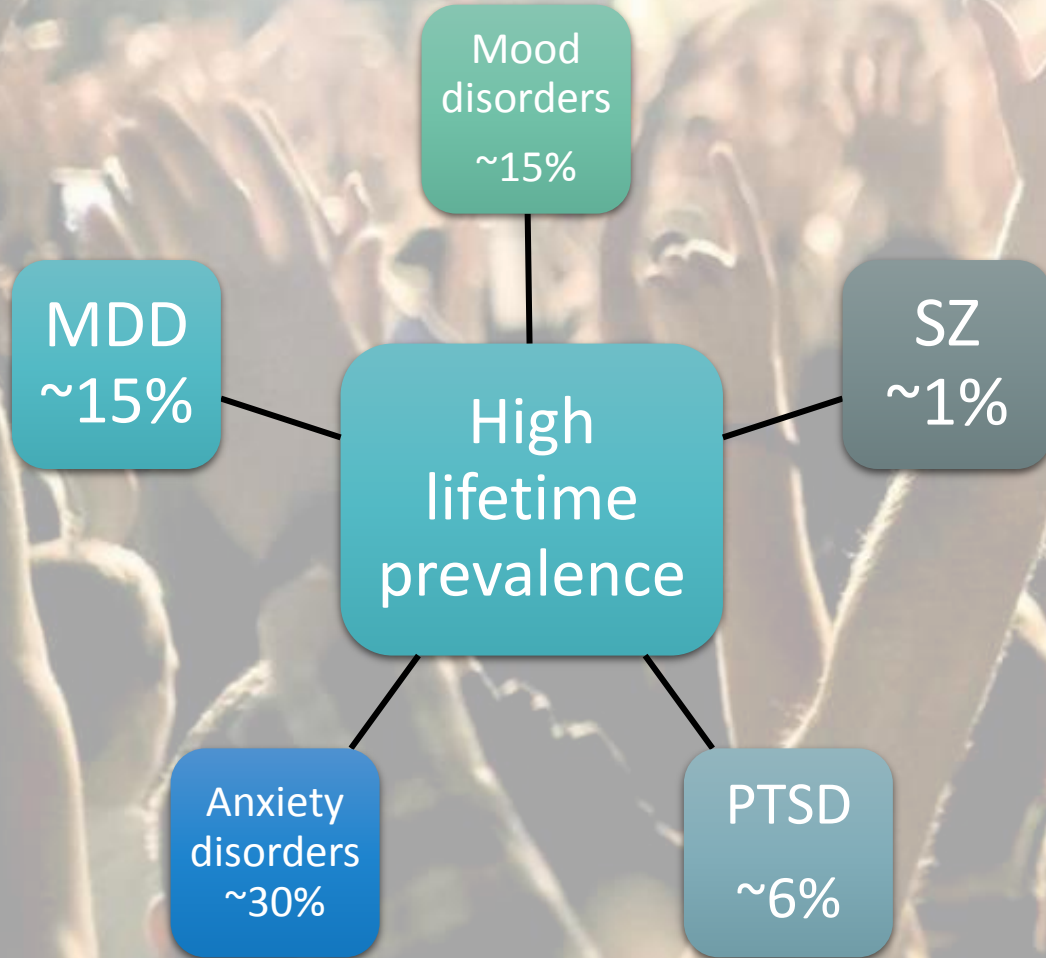
Transformed the way I thought about my work: not only acquiring knowledge but applying this knowledge to address a global challenge

65.3 million people worldwide are forcibly displaced

ROUGHLY THREE TIMES THE POPULATION OF AUSTRALIA



Severe mental illness



Poor understanding of the mechanisms
Lack of effective treatments
Few interventions in high risk individuals
Poor prognosis

Mental illness in refugees



- High prevalence of mental illness compared to the general population
- Extreme stress exposure
 - War related trauma + post-migration stress
- Post-traumatic stress reactions in refugees
 - May persist and even increase over time
 - Significant burden for individuals, families, and host societies
- **Substantial differences in how individuals respond to extreme stress**
 - *While some refugees develop psychopathology, majority are resilient*

Post-traumatic Stress Disorder (PTSD)

- **High risk exposure**
 - War and combat, physical attack or assault, life threatening incidences (Kessler & Wang, 2008)
- **Moderately heritable**
 - Epigenetic changes playing a major role
- **In parental PTSD :**
 - Offspring outcomes are thought to be moderated by the type of trauma
 - Offspring have differences in internalising problems and stress hormone dysregulation (Leen-Feldner et al., 2013)

Trauma is the key factor to PTSD and increases the susceptibility to mental and general health disorders in exposed individuals as well as their non-exposed offspring

Heritability of developing PTSD



Twin studies

Vietnam Era Twin Registry: True et al
1993

Civilian twin study: Stein et al, 2002

Genetic contribution

is about 28-45%
(heritability)



Recent large scale genome-wide association study of PTSD

Success was limited in
identifying the heritable genes

Broad types and timings of
trauma exposures → lead to
different biological effects
(subtypes)

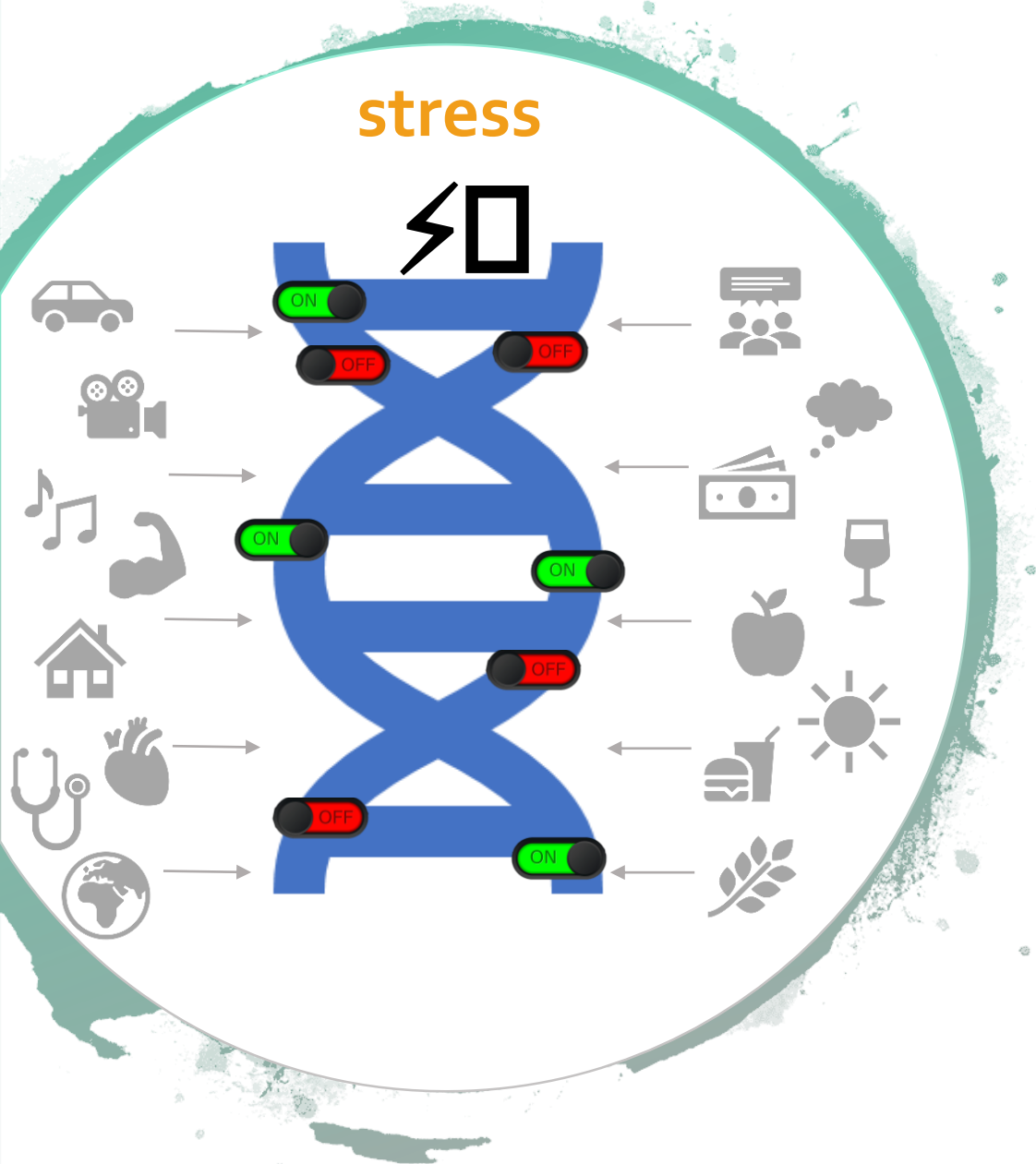
Effects diluted



More investigation needed

looking into more refined
populations and types of
trauma exposure

A role of epigenetics



Heritability of mental illness is about 30-40%

- Genes x Environment → risk/resilience

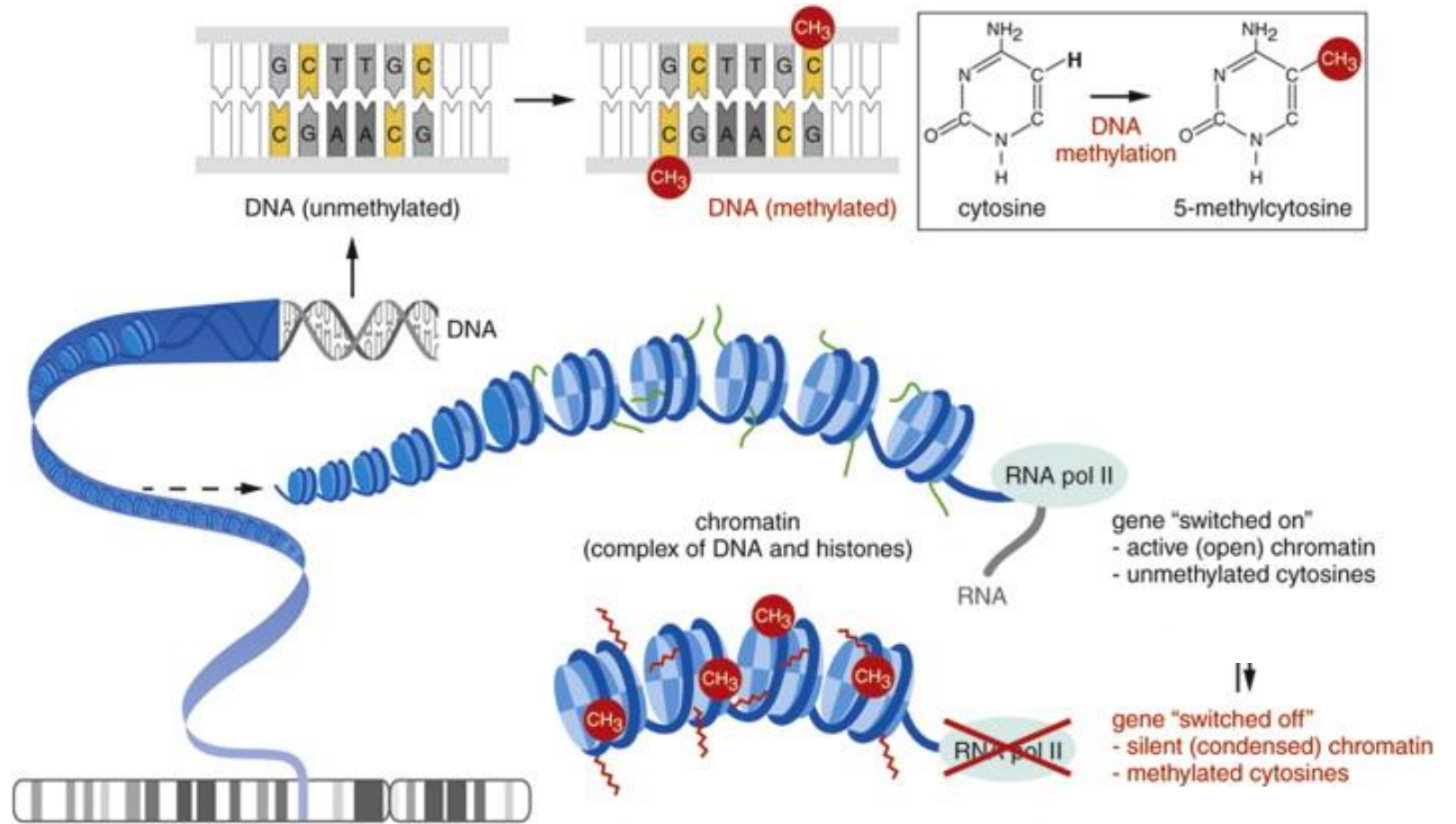
Epigenetics

- The primary molecular mechanism explaining how genes and environment interact

What are these chemical changes?



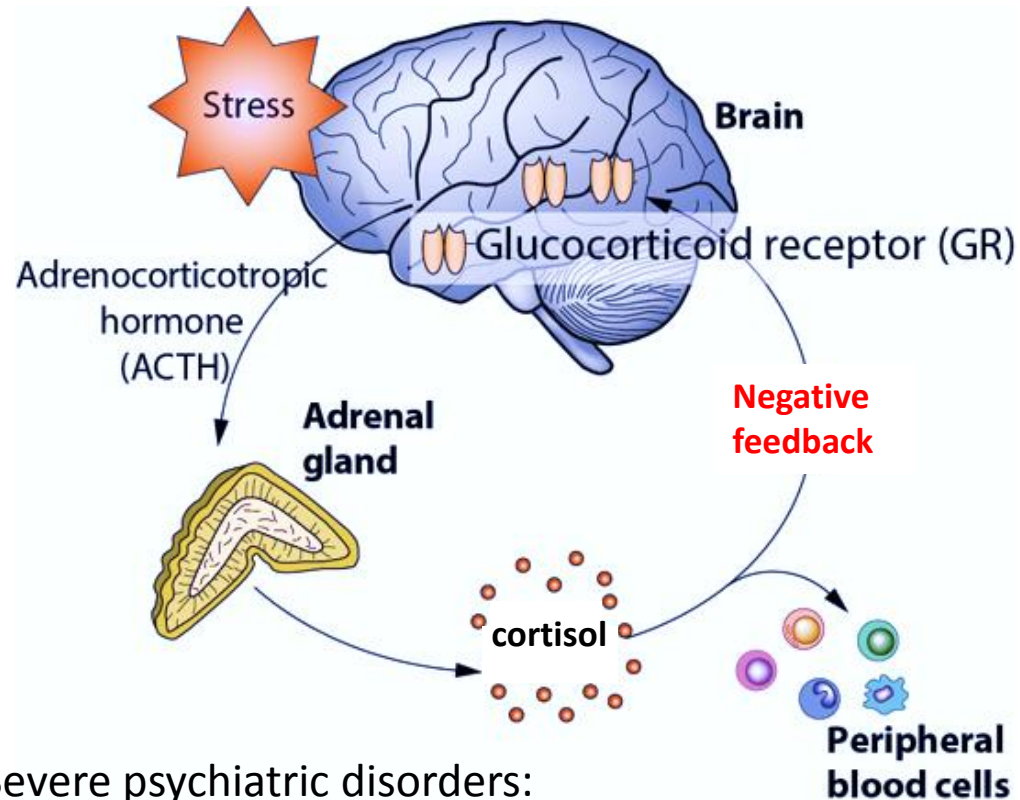
- Epigenetics involves many different types of modifications to the DNA, short vs long-lasting
- DNA methylation (DNAm) is one type:
 - addition of methyl group to DNA at CpG sites
- Amount of gene expression is proportional to amount of DNA methylation



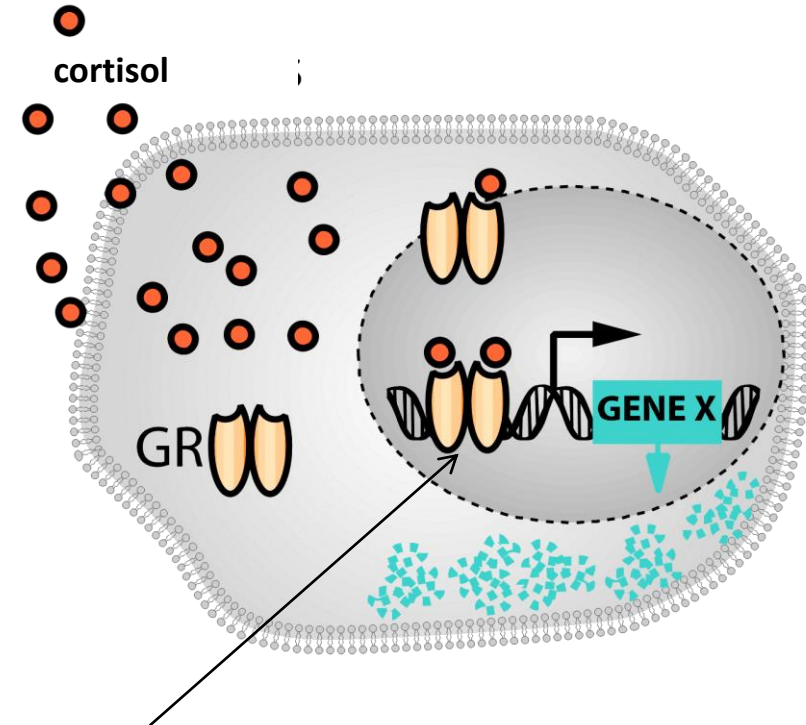
DNAm = gene silencer!

Stress hormone system

Mediates response to environment



Severe psychiatric disorders:
impaired negative feedback
→ System fails to shut down



Glucocorticoid response elements (GREs)

- transcriptome-wide response in gene expression
- **DNA de-methylation** → long lasting effects on gene expression in response to stress

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RISK or RESILIENCE
TO MENTAL ILLNESS

Swedish Famine
Dutch Hunger Winter
Holocaust

stress



Persistent epigenetic changes

Value of parent-offspring studies

Family based studies are more valuable than case-control design

Analysis of parent of origin effects

Whether a molecularly inherited effect is more detrimental if it is inherited from the mother or the father

Control for population stratification

Phenomenon impacts on case-control design

Families vastly share their environment

i.e. When assessing effects of traumatic experiences not shared by the whole family, but are inherited and coded in the genome

Summary

1

Evident gaps in knowledge about what makes individuals exposed to traumatic experiences vulnerable to mental health problems

2

Unknown mechanisms of how mental health problems are propagated to future generations

3

Holds promise for identifying people at risk (using biomarkers) to improve their resilience

4

Addresses a problem area in psychiatry: moving from symptom-based diagnosis towards mechanism-based diagnosis



TRIP:
The Refugee
Intervention Project



TRIP's overall mission

To improve mental health and economic outcomes in refugees and other traumatised people.

Specific aims

- To learn more about the biological risk factors for mental disorders caused by trauma
- To learn how these risk factors are transmitted through generations
- Identify psychological preventative/intervention strategies
- Use scientific discovery to reform migrant health policy

Major biological questions



- How does extreme stress raise risk to mental illness?



- What makes some individuals resilient to mental illness?

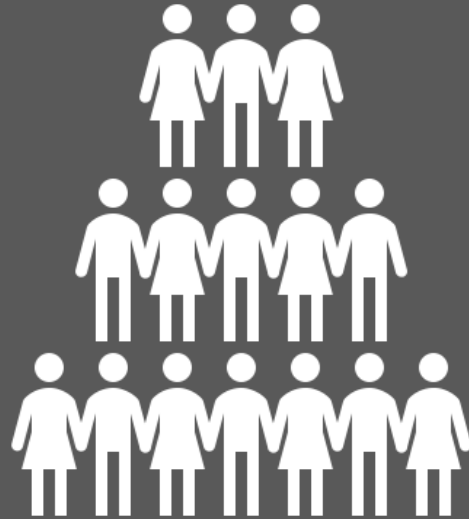


- How is this risk or resilience passed to offspring?



- How can we identify at-risk individuals and improve their resilience?

HISTORIC REFUGEES



+ AUSTRALIAN BORN OFFSPRING



Sydney and
Wollongong

Historical refugees from Croatia and Bosnia Herzegovina

Sydney area: 15,000 families

>20% first generation

+ arrived with refugee status after WWII or Yugoslav war

INNOVATIVE APPROACH

1. Focus on the long-term effects of trauma in a culturally and genetically homogenous group
2. Over 50x larger sample size than previous studies of traumatized populations
3. Using cutting edge techniques: next generation sequencing

+ BUILDING RESEARCH INFRASTRUCTURE

- world-first bank of unique biological and psychological data

Trauma exposures

50s/60s, post WWII

- Battles on Yugoslavian territory were considered the most violent
- illegal exit across the border in face of communist oppression and persecution
- Spending time in refugee camps across Europe and insecurity involved in refugee registration
- Long journey to Australia, 2-3 months by ship
- In Australia: lack of government services, no translation services, loneliness, inability to travel back to Yugoslavia (never see family again), social isolation, prejudice due to assimilation policy and attitudes of the time

1990s, Yugoslav war

- More pronounced experience of war trauma
- Imprisonment, torture, rape
- Some involved in the Siege of Sarajevo (5 April 1992 – 29 Feb 1996)
- Though government services were more sophisticated, still social and language isolation, loneliness and survivors guilt



- **Psychological assessments**

- Assessment of trauma exposure
- Substance abuse and lifestyle factors

OUTCOMES



- Identify the molecular signatures of risk and resilience to trauma



- Design appropriate interventions/treatments
- Identify who could benefit



- **Analyses for key questions**

1. Parents → sustained DNA methylation changes
2. Offspring → same changes as the parents
3. Identify biomarkers for development

collect
an

ation)

Team

Neurobiologists/neurogeneticists

- Molecular signature of trauma
- Lab work flow/analyses of molecular measures

Dr Natalie Matosin (UOW)



A/Prof Sibylle Schwab (UOW)



A/Prof Lezanne Ooi (UOW)



Prof Elisabeth Binder (Max Planck)



Marijeta [Maz] Miller



Dr Thorhildur Halldorsdottir (Iceland)



Psychologists

- Clinical evaluations
- Socio-economic info/demographics
- Integration of biology and psychology
- Long-term: interventions

Dr Kristina Kalfic



Dr Glenn Mitchell (UOW)



Health Policy Experts

- Identify policy recommendations

+ Key collaboration with STARTTS

- Dr Shakeh Momartin
- Jorge Aroche
- Mariano Coello

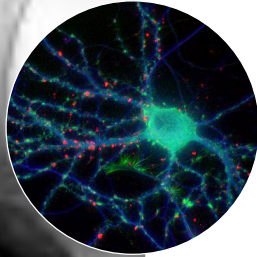


Future Directions

nmatosin@uow.edu.au



Define and refine the biological fingerprint of trauma



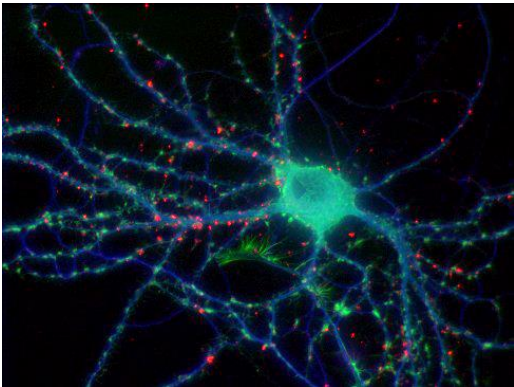
Expand into other levels of molecular regulation

- Combining genetics, gene expression and epigenetics



Develop biomarkers

- Important for identifying who is at risk and how we can improve their resilience



Questions

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Psychological Assessment process

