Developmental origins of mental health: new insights into mechanisms and interventions
Mental Health – do the roots lie mainly in the past?

Evolutionary Psychology

To a first approximation: our modern skulls house a stone age mind.
Or the present?

- 91% of 16-24 year olds use the internet for social networking
- Social media has been described as more addictive than cigarettes and alcohol
- Rates of anxiety and depression in young people have risen 70% in the past 25 years
- Social media use is linked with increased rates of anxiety, depression and poor sleep
- Cyber bullying is a growing problem with 7 in 10 young people saying they have experienced it
- Social media can improve young people’s access to other people’s experiences of health and expert health information
- Those who use social media report being more emotionally supported through their contacts
Or somewhere in between?
Development: does that mean that the underlying mechanisms are genetic?

“To understand the molecular mechanisms of depression, collect genetic data from more than 100,000 people” says Steven Hyman

Nature 13 Nov 2014. Special issue on depression
The Dutch Hunger Winter 1944/5
Later consequences of famine exposure at different gestational periods

<table>
<thead>
<tr>
<th>Young adult</th>
<th>Early</th>
<th>Mid</th>
<th>Late</th>
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</thead>
<tbody>
<tr>
<td>• cong. neural def.</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>• ♂ obese</td>
<td></td>
<td>+</td>
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</table>

<table>
<thead>
<tr>
<th>40-60 years</th>
<th>Early</th>
<th>Mid</th>
<th>Late</th>
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<tbody>
<tr>
<td>• brain anomalies</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• schizophrenia</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>• antisocial person.dis</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>• major affective disorder</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>• depressive symptoms</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>• ↓ perceived mental health</td>
<td>+</td>
<td>+</td>
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| • ♀ obese | +     |      | +    |
| • atherogenic lipid profile | + (?) |      |      |
| • BP ↑ low protein % |       |      | +    |
| • BP ↑ after stress |       | +   |      |
| • coronary heart disease |       | +   |      |
| • impaired glucose tolerance | +     | +   | + (?) |
| • micro albuminuria |       | +   |      |
Genetic

Epigenetic

Developmental Environment
Mechanisms of epigenetics

HES1 methylation at birth and childhood neuropsychological function.

Wechsler Pre-School and Primary Scale of Intelligence (WPPSI IQ) at age 4 years.

Spatial span length at age 7 years

Delayed matching to sample at age 7 years

Infant externalising score at age 1yr
Prenatal unhealthy diet, insulin-like growth factor 2 gene (*IGF2*) methylation, and attention deficit hyperactivity disorder symptoms in youth with early-onset conduct problems

Jolien Rijlaarsdam,1,2 Charlotte A. M. Cecil,3 Esther Walton,3 Maurissa S. C. Mesirow,3 Caroline L. Relton,4 Tom R. Gaunt,4 Wendy McArdle,5 and Edward D. Barker3

**Background:** Conduct problems (CP) and attention deficit hyperactivity disorder (ADHD) are often comorbid and have each been linked to ‘unhealthy diet’. Early-life diet also associates with DNA methylation of the insulin-like growth factor 2 gene (*IGF2*), involved in fetal and neural development. We investigated the degree to which prenatal high-fat and -sugar diet might relate to ADHD symptoms via *IGF2* DNA methylation for early-onset persistent (EOP) versus low CP youth. **Methods:** Participants were 164 youth with EOP (*n* = 83) versus low (*n* = 81) CP drawn from the Avon Longitudinal Study of Parents and Children. We assessed if the interrelationships between high-fat and -sugar diet (prenatal, postnatal), *IGF2* methylation (birth and age 7, collected from blood), and ADHD symptoms (age 7–13) differed for EOP versus low CP youth. **Results:** Prenatal ‘unhealthy diet’ was positively associated with *IGF2* methylation at birth for both the EOP and low CP youth. For EOP only: (a) higher *IGF2* methylation predicted ADHD symptoms; and (b) prenatal ‘unhealthy diet’ was associated with higher ADHD symptoms indirectly via higher *IGF2* methylation. **Conclusions:** Preventing ‘unhealthy diet’ in pregnancy might reduce the risk of ADHD symptoms in EOP youth via lower offspring *IGF2* methylation. **Keywords:** DNA methylation; Avon Longitudinal Study of Parents and Children; diet; conduct problems; attention deficit hyperactivity disorder; *IGF2*.

Five observational studies were included in the meta-analysis. The pooled adjusted odds ratio was 1.47 (95 % CI 1.24–1.74). The results support an increased risk of autism spectrum disorder in children of women who were obese during pregnancy. However, further study is warranted to confirm these results.
Prenatal Stress

Traumatic war experiences, natural disasters, death of husband

Repetative experimental stressors

Human evidence

Animal studies

Elevated risk of schizophrenia in children

Schizophrenia-like phenotype in the offspring (cognitive deficits, disrupted social behaviour, hyperactivity)

Molecular changes in the brain
- Altered DNA methylation in prefrontal cortex
- Disrupted maturation of prefrontal cortex
- Impaired HPA axis regulation
- Impaired synaptic plasticity

Are molecular changes regulated by epigenetic mechanisms that were disrupted during prenatal life?

Altered miRNA expression? Other epigenetic changes?
Table 3. Generalized linear models for the association of prenatal socioeconomic adversity and HSD11B2 methylation.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low maternal education</td>
<td>-10.9 (1.0)**</td>
<td>-8.8 (1.0)*</td>
</tr>
<tr>
<td>Maternal poverty</td>
<td>-4.5 (1.0)+</td>
<td>-4.5 (1.0)</td>
</tr>
<tr>
<td>Single mother</td>
<td>-4.5 (1.0)+</td>
<td>-2.3 (1.0)</td>
</tr>
<tr>
<td>Crowded dwelling</td>
<td>-2.3 (1.1)</td>
<td>-2.3 (1.1)</td>
</tr>
<tr>
<td>Prenatal tobacco use</td>
<td>-8.8 (1.0)*</td>
<td>-8.8 (1.0)+</td>
</tr>
<tr>
<td>Cumulative risk score</td>
<td>-2.3 (1.0)*</td>
<td>-2.3 (1.0)+</td>
</tr>
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Note: Each socioeconomic factor was modeled as the independent variable associated with HSD11B2 methylation extent as the dependent variable. Beta coefficients represent percent change in methylation per unit difference in socioeconomic adversity. Adjusted models control for maternal age, prepregnancy BMI, race, infant sex and birth weight percentile. n = 444; additional exclusions were made for poverty and cumulative risk score variables (n = 403). + p<0.10, * p<0.05, ** p<0.01.

Grand-maternal smoking in pregnancy and grandchild’s autistic traits and diagnosed autism

Jean Golding¹, Genette Ellis¹, Steven Gregory¹, Karen Birmingham¹, Yasmin Iles-Caven¹, Dheeraj Rai² & Marcus Pembrey¹

Although there is considerable research into the genetic background of autism spectrum disorders, environmental factors are likely to contribute to the variation in prevalence over time. Rodent experiments indicate that environmental exposures can have effects on subsequent generations, and human studies indicate that parental prenatal exposures may play a part in developmental variation. Here we use the Avon Longitudinal Study of Parents and Children (ALSPAC) to test the hypothesis that if the mother or father (F1) had been exposed to their own mother’s (F0) smoking during pregnancy, the offspring (F2) would be at increased risk of autism. We find an association between maternal grandmother smoking in pregnancy and granddaughters having adverse scores in Social Communication and Repetitive Behaviour measures that are independently predictive of diagnosed autism. In line with this, we show an association with actual diagnosis of autism in her grandchildren. Paternal grandmothers smoking in pregnancy showed no associations.

Figure 5.1 Life course model of Non Communicable Disease (NCD) prevention, showing the importance of intervention in adolescents and young adults.
GETTING HEALTHY BEFORE PREGNANCY, FOR PREGNANCY

- have a Body Mass Index (BMI) that is **18.5 to 24.9**
- eat a healthy diet which includes folic acid
- be physically active
- address mental health problems
- stop smoking
- avoid alcohol and recreational drugs

In 2013/14 there were about twice as many referrals for psychological therapy in women aged 15–24 as in men.\(^6\)
Maternal mental health before and during pregnancy is a particular cause of concern,\(^7\)\(^-\)\(^9\),\(^10\)\(^,\)\(^11\) representing a further opportunity for improving the health of women.
Box 5.2 Quote from mother, aged 30

‘I don’t know, you just assume that you just get pregnant and then you go to your GP and everything falls in place from there. I didn’t know that there were things that you should be doing prior to becoming pregnant. You don’t really plan it... although I was planning it.’

Source: Barrett G. Why do women invest in pre-pregnancy health and care? A qualitative investigation with women attending maternity service. BMC Pregnancy and Childbirth 2015:
Box 5.3 The wish to be good parents

‘Some time ago, I asked to meet a group of 15 year old pupils in one of Birkenhead’s most challenged schools… I asked each of them to list for me which six outcomes they most wanted to gain for themselves from attending school.

‘Their replies both shocked and delighted me. Without exception, all of these young citizens stated that they wanted their school to be a safe place, to help teach them what was involved in building long-term friendships and to equip them with the necessary skills to gain a good job. Most surprisingly, all of the pupils listed as one of their remaining requests the wish to be taught how to be good parents.’

Summary

➢ DOHaD research confirms the importance of early life environment to neurocognitive development & mental health
➢ A range of factors, many of which are avoidable, are implicated, including under- and overnutrition, obesity, stress, smoking and environmental toxicants
➢ The heritable nature of underlying processes is not simply via fixed genetics, but epigenetic mechanisms involved in developmental plasticity
➢ These may provide early biomarkers of risk and for assessing efficacy of interventions
➢ A life course approach emphasises the importance of interventions in the preconception period, e.g. in adolescents
➢ Such interventions need to be developed with young people themselves, to generate motivation and demand for services and support
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