WHAT DOES THE ENGLISH AND ROMANIAN ADOPTEES STUDY HAVE TO SAY ABOUT THE CAUSES OF ADHD?

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Royal College of Psychiatrists – Neurodevelopmental SIG 2019
• Extraordinary environments, extreme plasticity and ADHD.

• Isolating maltreatment effects – English & Romanian Adoptees study.

• The effect of early deprivation on adult brain structure & function.

• ADHD as a core clinical feature of institutional deprivation.

• Adult deprivation-related ADHD is mediated by brain alterations.

• Deprivation-related ADHD – co-occurring features and impairment.
<table>
<thead>
<tr>
<th></th>
<th>Lecturer</th>
<th>Consultancy</th>
<th>Research Grant</th>
<th>Royalties</th>
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<tr>
<td>Shire</td>
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<td>Neurotech solutions</td>
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<td>New Forest Parenting Package</td>
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<td>MRC, ESRC, NIHR, Wellcome Trust, TWF, MQ</td>
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<td>KU Leuven U of Copenhagen</td>
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EXTRAORDINARY ENVIRONMENTS,
EXTREME PLASTICITY AND ADHD.
ADHD RUNS IN FAMILIES (G) AND CREATE ENVIRONMENTS (E)

Both G and E are *correlated* with ADHD

Sonuga-Barke & Harold, 2018; Demitos et al., 2017
DIFFICULT CIRCUMSTANCES CLUSTER IN FAMILIES

- Social Disadvantage
- Less Healthy Lifestyle
- Poor Mental Health
- Parenting Challenges
- Family Stress
- Disorganised Household
- Discord & Breakdown
- Educational Underachievement

Small and non-deterministic reciprocal relations
ADHD IS MORE PREVALENT IN THOSE FAMILIES

- EDUCATIONAL UNDERACHIEVEMENT
- SOCIAL DISADVANTAGE
- LESS HEALTHY LIFESTYLE
- DISCHORD & BREAKDOWN
- POOR MENTAL HEALTH
- DISORGANISED HOUSEHOLD
- FAMILY STRESS
- PARENTING CHALLENGES

Small and non-deterministic reciprocal relations
PARENTS PASS ON GENES (G) AND CREATE ENVIRONMENTS (E)

Both G and E are correlated with ADHD.

Sonuga-Barke & Harold, 2018; Demitos et al., 2017

Twin studies suggest 70% is due to shared g G - 0% to shared E

ORDINARY REARING ENVIRONMENTS PROBABLY PLAY A MARGINAL & SUBTLE ROLE IN ADHD AETIOLOGY
Heritability estimates are constrained by the range of environmental exposures experienced.

Those derived from ordinary populations can say little about the impact of extraordinary environments.

What could be the mechanism underpinning the effects of extraordinary environments?

Under normal circumstances plasticity allows the environmental regulation of genetic processes to mould the brain in complex & subtle ways to bring about learning and development.

Could extraordinary environments produce such extreme plasticity that they overrides genetic risk?

Can extraordinary adverse environments do such *bad* they derail development in an otherwise genetically strong brain?

Can extraordinary enriched environments do such *good* they put development back-on-track in an genetically at risk brain?
Recent meta-analyses identified associations between early maltreatment and later brain development.

- Reduced grey and white matter volume.
- Cortical thinning of key areas.
- Alterations in sub-cortical regions – especially limbic system.
- Reduced integrity of vital white matter tracts (e.g., corpus collosum).

Teicher et al. 2016

Systematic exposure of children to maltreatment obviously impossible for ethical reasons.

Many studies therefore have fundamental methodological flaws that frustrate causal inference.

- Retrospective reports of exposures.
- Selection by outcome (participants included when referred for disorders).
- Familial confounding between exposure and brain structure (i.e., genes and environment are correlated).
WHY ARE MAL & BRAIN CORRELATED?

IT'S COMPLICATED AS BOTH ARE FAMILIAL.

THIS BRINGS IN THE COMPLICATION OF GENETIC FACTORS

GENE COULD OPERATE DIRECTLY...

...WHILE ALSO SHAPING THE CONTEXT FOR MAL

THIS MEANS THAT MALTREATMENT COULD ACTUALLY BE SHAPING THE BRAIN OR SIMPLY BE A CORRELATED FEATURE OF GENETIC EFFECTS ON THE BRAIN.

...AND CREATING A MISLEADING CORRELATION WITH BRAIN
Are there situations where familial confounding doesn't cloud the issue?

Extraordinary non-familial adverse environments?

Institutional deprivation could they induce extreme brain plasticity sufficient to override G?

Could these cause ADHD?
ISOLATING MALTREATMENT EFFECTS – ENGLISH & ROMANIAN ADOPTEES STUDY.
THE CONDITIONS IN THE ROMANIAN ORPHANAGES WHEN THE CEAUȘESCU REGIME FELL

- Severely restricted diet
- High rates of communicable disease
- Little social/cognitive stimulation
- No personalised care – no chance to establish selective attachments

HOW DID THIS ACTUALLY IMPACT DEVELOPMENT?
ENGLISH & ROMANIAN ADOPTEES TEAM

- Robert Kumsta
- Wolff Schlotz
- Jana Kreppner
- Barbara Maughan
- Mark Kennedy
- Nicky Knights

- Graeme Fairchild
- Sagari Sarkar
- Jonathan Hill
- Jonathan Mill
- Hanna Kovshoff

*Department of Health, MRC, Nuffield Foundation, ESRC, Jacobs Foundation.*
RATIONALE AND DESIGN OF A UNIQUE NATURAL EXPERIMENT

ADOPTION OF PROFOUNDLY DEPRIVED INFANTS FROM THE ROMANIAN ORPHANAGES

PRE-1990’s

RADICAL AND PRECISELY TIMED CHANGE

SEVERELY RESTRICTED DIET - LITTLE SOCIAL OR COGNITIVE STIMULATION
1 TO 43 MONTHS

Deprivation duration likely un-confounded with genetic risk

ADOPTION

NURTURING, SUPPORTIVE FAMILY
25 TO 28 YEARS

165 of 324 children processed by the Home Office between Feb ’90 & Sept ’92. 21 straight from families no institutional deprivation. 52 UK adoptees.

Followed up at ages 4, 6, 11 and 15 and in young adulthood.
THE GENETIC SCORE FOR INTER-CRANIAL VOLUME IS UNCORRELATED WITH DEPRIVATION DURATION

$R = 0.06; p = 0.56$
THE GENETIC SCORE FOR ADHD IS UNCORRELATED WITH THE DEPRIVATION DURATION
# Young Adult Sample

<table>
<thead>
<tr>
<th>Category</th>
<th>N</th>
<th>%</th>
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<tbody>
<tr>
<td>Young Adult &amp; Parent</td>
<td>130</td>
<td>59.9</td>
</tr>
<tr>
<td>Parent only</td>
<td>23</td>
<td>10.6</td>
</tr>
<tr>
<td>Young adult only</td>
<td>11</td>
<td>5.1</td>
</tr>
<tr>
<td>Participants with data</td>
<td>164</td>
<td>75.6</td>
</tr>
<tr>
<td>Brain imaging analysis</td>
<td>88</td>
<td>47.7</td>
</tr>
<tr>
<td></td>
<td>No ID (UK)</td>
<td>ID (Rom)</td>
</tr>
<tr>
<td>--------------------------</td>
<td>------------</td>
<td>----------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 6 months</td>
</tr>
<tr>
<td>n</td>
<td>21</td>
<td>21</td>
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<tr>
<td>Percentage original sample</td>
<td>40.4%</td>
<td>36.2%</td>
</tr>
<tr>
<td>Mean age (SD) [years]</td>
<td>24.4 (1.0)</td>
<td>24.5 (0.9)</td>
</tr>
<tr>
<td>Percentage female</td>
<td>38.1%</td>
<td>42.9%</td>
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</table>
### IMAGING BATTERY

#### BRAIN STRUCTURE
- Voxel and Surface-based Morphometry

#### BRAIN FUNCTION
- Inhibition: *SSP*
- Reward: *MID*
- Empathy: *EAT*
- Emotion Processing: *NimStim*

#### CONNECTIVITY
- Diffusion Tensor Imaging
- Resting State Connectivity

#### NEUROPSYCHOLOGY
- Inhibition: *GNG*
- Risk Taking: *RCT*
- Prospective Memory: *EAT*
- Emotion Processing: *EBT*
THE EFFECT OF EARLY DEPRIVATION ON ADULT BRAIN STRUCTURE & FUNCTION.
ADULT BRAIN STRUCTURE
WE KNOW HC RECOVERED OVERALL AFTER A DEVASTATING INITIAL IMPACT

ARRIVE IN THE ADOPTIVE HOME

DOES CHILDHOOD DEPRIVATION HAVE AN ENDURING EFFECT ON BRAIN VOLUME?
DOES CHILDHOOD DEPRIVATION HAVE AN ENDURING EFFECT ON BRAIN VOLUME?

THIS EFFECT REMAINED SIGNIFICANT AFTER CONTROLLING FOR A RANGE OF POTENTIAL CONFOUNDERS.

BIRTH WEIGHT, SUB-NUTRITION, HEIGHT, GENETIC RISK FOR A SMALL HEAD.
THREE LOCALISED CORTICAL EFFECTS OF DEPRIVATION

- Reduced right inferior frontal with ID
- Spared right inferior temporal with ID
- Spared right medial orbital with longer ID

<table>
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<tr>
<th>surface area</th>
<th>thickness</th>
<th>volume</th>
<th>overlap</th>
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BUT NO EFFECTS ON CORE LIMBIC REGIONS
ADHD AS A CORE CLINICAL FEATURE FOLLOWING DEPRIVATION
ADHD SYMPTOMS TO MID-ADOLESCENCE

Stevens et al., 2010
ADHD SYMPTOMS TO ADULTHOOD

inattention/hyperactivity

Kennedy et al., 2017
Is there an unusually high persistence and continuity in deprivation-related ADHD?

Is there a distinctive pattern of subtype/comorbidity/sex ratio/impairment?
ADULT ADHD DIAGNOSIS

% CASES

<table>
<thead>
<tr>
<th></th>
<th>HYPER/IMPULSIVE</th>
<th>INATTENTIVE</th>
<th>COMBINED</th>
<th>ANY PRESENTATION</th>
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<tbody>
<tr>
<td>UK</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;6</td>
<td></td>
<td></td>
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</table>
• DSM-5 “child” thresholds at both time points.
• Severe impairment – CAPA “definite”; CBRS “always” in at least 2 settings.
ADULT ONSET AND OFFSET

ADHD+ → ADHD+ (72.2%)
ADHD+ → ADHD- (27.8%)
ADHD+ → ADHD+ (61.9%)
ADHD+ → ADHD- (38.1%)

AGE 15
YAF
AGE 15
YAF
ARE ONSET REALLY NEW CASES?

AVERAGE SCORE PER ITEM (RUTTER/DSDQ)

PERSISTERS
NEW CASES
NEVER ADHD
SEX RATIO & PRESENTATION

FEMALES

AGE 15

YOUNG ADULT

PREDOMINANTLY INATTENTIVE

AGE 15

YOUNG ADULT
ADULT DEPRIVATION-RELATED ADHD IS MEDIATED BY BRAIN ALTERATIONS.
A NEURAL PATH BETWEEN DEPRIVATION AND ADHD & IQ
DEPRIVED INDIVIDUALS WITH SPARED ITG HAD LOWER ADHD SYMPTOMS
DEPRIVATION-RELATED ADHD
CO-OCCURRING FEATURES AND IMPAIRMENT.
## CO-OCCURING CONDITIONS

<table>
<thead>
<tr>
<th></th>
<th>LoRisk</th>
<th>HiRisk</th>
<th>ADHD-</th>
<th>ADHD+</th>
<th>LoR vs ADHD+</th>
<th>ADHD- vs ADHD+</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sig p</td>
<td></td>
</tr>
<tr>
<td>DSE</td>
<td>0.1 (0.63)</td>
<td>1.0 (1.58)</td>
<td>1.6 (1.84)</td>
<td>.004</td>
<td>NS</td>
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<tr>
<td>Quasi-autism</td>
<td>1.3 (2.14)</td>
<td>1.8 (2.45)</td>
<td>5.3 (4.18)</td>
<td>.001</td>
<td>&lt;.001</td>
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<tr>
<td>IQ</td>
<td>102 (16.09)</td>
<td>96 (13.11)</td>
<td>93 (10.62)</td>
<td>.06</td>
<td>NS</td>
<td></td>
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<tr>
<td>CD</td>
<td>46.4 (10.7)</td>
<td>48.4 (13.4)</td>
<td>51.4 (11.1)</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>CU</td>
<td>26.0 (7.0)</td>
<td>26.7 (7.91)</td>
<td>35.8 (6.30)</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
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DISINHIBITED SOCIAL ENGAGEMENT

<table>
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<tr>
<th>Individual symptoms</th>
<th>UK</th>
<th>&lt;6</th>
<th>&gt;6</th>
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<tr>
<td>Too friendly</td>
<td>5</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Personal comments</td>
<td>10</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Unaware of social boundaries</td>
<td>15</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Excessive disclosure</td>
<td>15</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Not stranger aware</td>
<td>10</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

DSE present
DISINHIBITED SOCIAL ENGAGEMENT

Any self-report disinhibition

Any observer rated disinhibition

% CASES

LoDep  DSE-  DSE+

0  5  10  15  20  25  30  35  40  45
QUASI-AUTISM

PERCENT SYMPTOMS ENDORSED

SOCIAL RECIPROCAL INTERACTION

COMMUNICATION

REPETITIVE & STEREOTYPED BEHAVIOURS

AGE 6  AGE 11  AGE 15  YAF  AGE 6  AGE 11  AGE 15  YAF  AGE 6  AGE 11  AGE 15  YAF
IS ADHD PART OF A DEPRIVATION SYNDROME

LOW RISK – LOOSELY RELATED

HIGH RISK – MORE TIGHTLY RELATED
PSYCHO-SOCIAL FUNCTIONING

LOW DEP
UNEMPLOYED
LIVING AT HOME
МARRIED/CO-HABIT

ADHD -
LIMITED EDUCATION

ADHD +

* *
WHAT DRIVES IMPAIRMENT (bivariate)

DSE
Beta=32 p=.001

QA
Beta=.48 p<.001

ADHD
Beta=.52 p<.001
WHAT DRIVES IMPAIRMENT (multivariate)

DSE

Beta=.40 p<.001

QA

Beta=.26 p=.005

ADHD

Beta=.40 p<.001
SUMMARY

• ID has deep seated effects on brain growth.
• These are not fully remediated by years of high quality care in adoptive homes.
• ADHD is a core clinical feature following ID.
• It is unusually persistent into adulthood where it drives impairment.
• Deprivation-related brain stunting and associated neuropsychological effects drive adverse effects on ADHD.
• The regional ITG sparing appeared compensatory in nature – reducing the negative effects of deprivation on ADHD.