How does adversity in childhood ‘get under the skin’

What can we learn from neuroscience and epigenetics?

Eamon McCrory
Professor of Developmental Neuroscience & Psychopathology, UCL
Consultant Clinical Psychologist, Anna Freud Centre
emccrory@ucl.ac.uk
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e.mccrory@ucl.ac.uk
A matter of pressing societal importance
...and a challenging scientific puzzle:

How does early adversity ‘get under the skin’ in ways that increase enduring vulnerability to mental and physical health problems across the lifespan?
Healthy development

Adversity

Poor outcomes

- Psychiatric disorders
- Attainment
- Economic productivity
- Physical Health

Infancy ............... Childhood ............... Adolescence ............... Adulthood
The theory of **Latent Vulnerability** is an emerging framework for thinking about possible mechanisms of vulnerability that increase risk of psychiatric disorder (McCrorry & Viding, 2015).
Genotype

Adverse environment

Response & adaptation...

- Low protective factors
- High stressors
- Risk genotypes

High risk of disorder

- High protective factors
- Low stressors
- Resilient genotypes

Low risk of disorder
Genetic / Epigenetic

Neurobiological

Cognitive

Behavioural

Maltreatment
Epigenetic ‘adaptation’

Epigenetics is the study of changes in gene expression without changes to the genes themselves.

*DNA methylation*: Methyl marks are added to certain DNA bases repressing gene activity.
Epigenetic instructions change how and when certain genes are turned on or off. By and large, epigenetic modulation serves adaptive regulatory processes.
Epigenetic modulation continues across the lifespan....

Fraga, Fraga et al., 2005

Methylation
Chromosome 1

Similar methylation levels
Hypo-methylation
Hyper-methylation

3 yrs old      50 yrs old
Twin 1 vs. Twin 2   Twin 1 vs. Twin 2

Anna Freud Centre
Animal Studies
Michael Meaney’s animal studies

Pups experiencing High Levels Licking Grooming

- Decreased startle response
- Increased open field exploration
- Better adaptation to novel environments
- Robust negative feedback in HPA axis

Pups experiencing Low Levels Licking Grooming

- Increased startle response
- More anxious in new surroundings
- Decreased HPA negative feedback
Demethylation of Nr3c1 exon

- Stress resilience
- High nurturing as mothers

Methylation of Nr3c1 exon

- Stress reactivity
- Low nurturing as mothers

Meaney & Szyf, 2005; Weaver et al., 2004; Hyman, 2009
Meaney & Szyf, 2005
Weaver et al., 2004
Hyman, 2009

High Nurturing

Demethylation of Nr3c1 exon

Adult Phenotype: Stress resilient
High nurturing as mothers
Epigenetics: Summary

• Developmental processes have evolved to be robust to a wide variety of experiences – epigenetic modification is though to help optimize functioning to the environmental conditions that a child is likely to face during their development. Caution is needed as to date most research has been conducted with animals.

• Epigenetic mechanisms have been postulated as one way early adversity ‘gets under the skin’ (e.g. Radtke et al, 2011; Oberlander et al., 2008, McGowan et al., 2009). In other words, epigenetic modulation following childhood adversity may embed latent vulnerability to future stressors that manifests later in life as mental and physical health problems.

• Many important questions remain: To what degree are epigenetic changes reversible? Does reversibility vary across genes, and interact with genotype and other environmental experiences? Are there key periods of vulnerability?
Brain Structure: Differences in children who have experienced maltreatment

For example:

- Reduced **grey matter volume** (GMV) in the left orbitofrontal cortex
- Reduced **cortical thickness** in an extended right frontal cluster
- Similar pattern for boys and girls
- Regions implicated in a variety of higher order emotional and cognitive processes, notably in social and emotional regulation and flexibility.
- Atypical structure in clinical samples of depressed and PTSD patients.
Brain Function: Differences in children who have experienced maltreatment

What are the neuro-cognitive mechanisms that embed latent vulnerability following childhood adversity?
Candidate mechanism 1:

Altered threat processing
Altered threat appraisal

Children exposed to physical maltreatment have been shown to have altered processing of angry faces:

- able to more accurately identify angry facial expressions using sparse perceptual information than peers
- devote more attentional resources to the processing of angry faces
- Interpreted as increased hypervigilance to threat

Pollak & Sinha, 2002, Pollak et al., 2001
Brief article

Development of perceptual expertise in emotion recognition

Seth D. Pollak a,*, Michael Messner a, Doris J. Kistler b, Jeffrey F. Cohn c

a Department of Psychology and Waisman Center, University of Wisconsin at Madison, 1500 Highland Avenue, Madison, WI 53711, USA
b University of Louisville, The Heuser Hearing Institute, 117 E. Kentucky Street, Louisville, KY 40203, USA
c University of Pittsburgh, 4327 Sennott Square, Pittsburgh, PA 15260, USA
What is the neural basis of altered face processing in maltreated children?
Who are the children in our studies?

Children exposed to maltreatment

- Aged 10-14 male and female
- Recruited from a London social services department
- Documented experiences of abuse, including neglect, physical, sexual and emotional abuse
- Vast majority show non-clinical presentation, although sub-clinical elevation in conduct and attentional problems

Control children recruited from London schools, matched for:

- Age – Pubertal stage – IQ – Gender – Ethnicity – Socioeconomic status
Heightened neural reactivity to threat in child victims of family violence

Eamon J. McCrory\textsuperscript{1,2,*}, Stéphane A. De Brito\textsuperscript{1,2,*}, Catherine L. Sebastian\textsuperscript{1}, Andrea Mechelli\textsuperscript{3}, Geoffrey Bird\textsuperscript{4,5}, Phillip A. Kelly\textsuperscript{1,2}, and Essi Viding\textsuperscript{1}
Current Biology

Heightened neural reactivity to threat in child victims of family violence

Eamon J. McCrory¹,²,*
Stéphane A. De Brito¹,²,*
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Heightened neural reactivity to threat in child victims of family violence

Eamon J. McCrory¹,²,*, Stéphane A. De Brito¹,²,*, Catherine L. Sebastian¹, Andrea Mechelli³, Geoffrey Bird⁴,⁵, Phillip A. Kelly¹,², and Essi Viding¹
Increased right amygdala reactivity and increased bilateral anterior insula reactivity to angry vs. calm faces in children exposed to family violence.

This may be a latent neural marker of latent vulnerability – the same neural signature is common in anxiety disordered populations (Etkin & Wager, 2007).
Left anterior insula activation was greatest in those children exposed to higher levels of family violence.
Exposure to family violence may ‘recalibrate’ responsiveness of the anterior insula and amygdala in processing potential threat.

But is this a conscious process? In other words, is this hypervigilance to threat under higher order regulatory influence?
Amygdala activation in maltreated children during pre-attentive emotional processing

Eamon J. McCrory, Stéphane A. De Brito, Philip A. Kelly, Geoffrey Bird, Catherine L. Sebastian, Andrea Mechelli, Sophie Samuel and Essi Viding
Cortex
“high road”

“low road”

Thalamus
LGN
Pulv

Amygdala

emotional stimulus

emotional response

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Amygdala
1. Is amgydala reactivity calibrated in response to environmental adversity?
Duration of abuse associated with amygdala response in children

McCrory et al., 2013
Severity of abuse associated with amygdala response in adults

$r^2 = 0.37$

Dannlowski et al., 2013
Collectively, these findings suggest that the responsiveness of the amygdala is calibrated and adapts to the degree of environmental threat.
2. Do higher levels of amygdala reactivity to threat predict future psychopathology?
Amygdala reactivity BEFORE stress predicts future symptoms

Admon et al., 2009
Prior amygdala reactivity to threat cues predicts anxiety and depression symptoms in a cohort of health adults (n=340) following future life stressors over a 1 – 4 year period.
3. Is altered amygdala reactivity to threat implicated in disorders associated with maltreatment?
YES - Heightened amygdala reactivity has been reliably associated with anxiety /depression in adolescents and adults

Monk et al., 2008
Therefore, increased threat-related amygdala reactivity following maltreatment may represent one discrete neurocognitive mechanism characterizing latent vulnerability – increasing psychiatric risk following exposure to future stressors.
Candidate mechanism 2:

Over-general autobiographical memory
Autobiographical memory (ABM)

- Autobiographical memory is concerned with the recollection of personally experienced events and plays a central role in scaffolding our sense of self.
- It is increasingly recognised as important in helping us to effectively negotiate the future.
- Children who have experienced maltreatment tend to show a pattern of overgeneral memory, such that they lack specificity when recalling events from their past. This may be due to the presence of traumatic events they wish to avoid.
- Overgeneral memory is associated with increased risk of depression and PTSD and may therefore represent another latent vulnerability mechanism.
ABM in children who have experienced maltreatment

In our current study preliminary results suggest that children who experience maltreatment relative to their peers show:

i. Increased over-general memory

ii. Altered brain activation when recalling positive and negative memories

When they recall POSITIVE memories they show reduced activation of the hippocampus, fusiform gyrus and inferior temporal gyrus

When they recall NEGATIVE memories they show higher activation of the middle temporal gyrus, parahippocampus and amygdala

McCrory et al., unpublished
Other candidate neurocognitive systems indexing Latent Vulnerability

1. Threat processing
2. Autobiographical memory
3. Emotion regulation
4. Reward processing / risk taking

Psychiatric Vulnerability
Latent Vulnerabilities

- Threat bias
- Autobiographical memory
- Emotion regulation

Outcome

Healthy

Unhealthy

Clinical Threshold

Maltreatment

Infancy ........... Childhood ........... Adolescence ........... Adulthood
Latent Vulnerabilities

- Threat bias
- Autobiographical memory
- Emotion regulation

Maltreatment

Clinical Threshold

Life Stressors

Infancy ............... Childhood ............... Adolescence ............... Adulthood
Infancy ....................................... Childhood ........................... Adolescence ........................... Adulthood

Healthy                           Unhealthy

Clinical Threshold

Maltreatment

Outcome

Unhealthy

Healthy
Summary & Implications

• We are beginning to learn how early adversity can calibrate genetic and neurocognitive systems in ways that may reflect adaptation to early risk environments but carry long term costs for physical and mental health.

• We need to learn much more about the specific neuro-cognitive mechanisms that underpin latent vulnerability.

• In the longer term, such understanding may help us:
  i. Develop mechanistically informed prevention strategies – to help prevent disorders BEFORE they emerge
  ii. Target help more effectively for those children who need it most
  iii. Refine our treatment approaches to psychiatric disorders for children who have experienced maltreatment – as depression and anxiety in these children may not necessarily be the same.
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