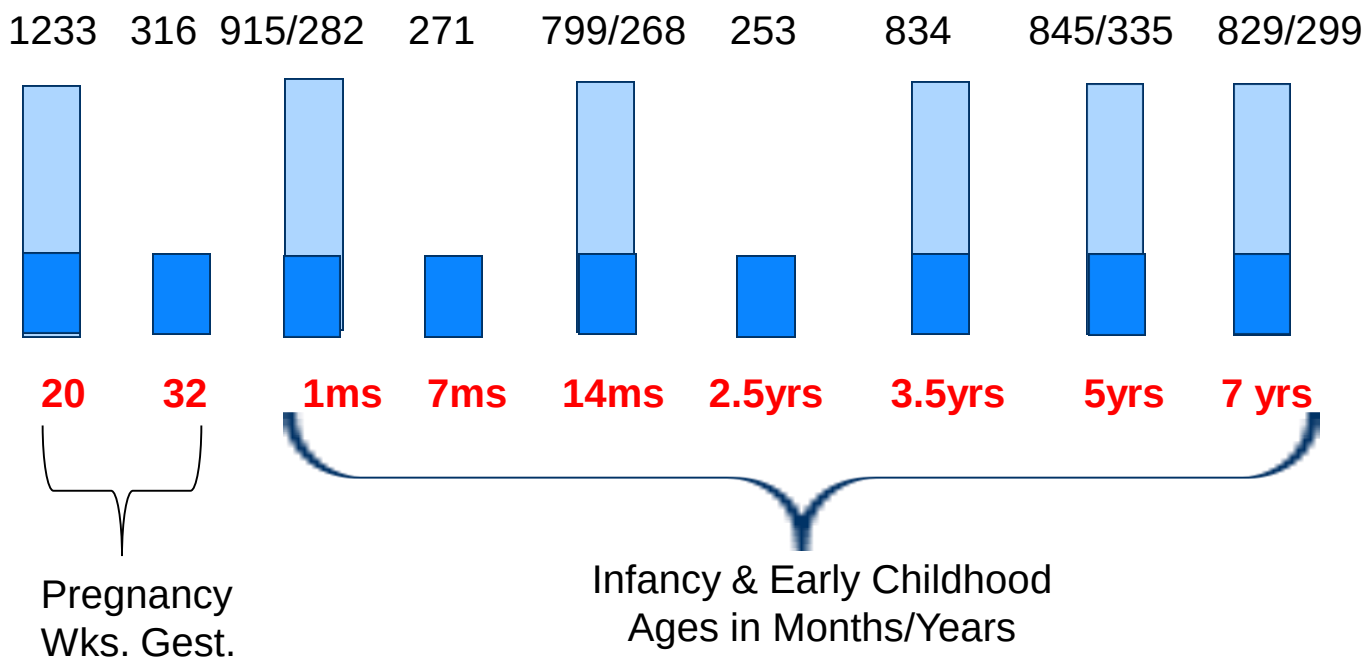
Sex differences in adaptation and pathways to psychopathology: recent findings from the Wirral Child Health and Development Study

Developmental Science , Liverpool, October 2017

Jonathan Hill, Helen Sharp, Andrew Pickles, Chris Murgatroyd, John Quinn, Nicola Wright

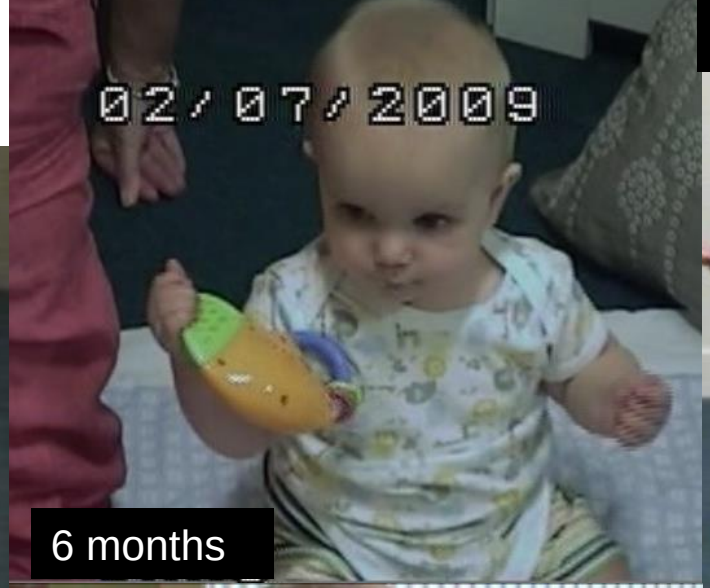
Wirral Child health and Development Study UK

Wirral Child Health & Development Study - Numbers



Sample details in Sharp et al (2012) PLOS One 10 (7) e45446


4 weeks



6 months


14 months


2.5 years


3.5 years

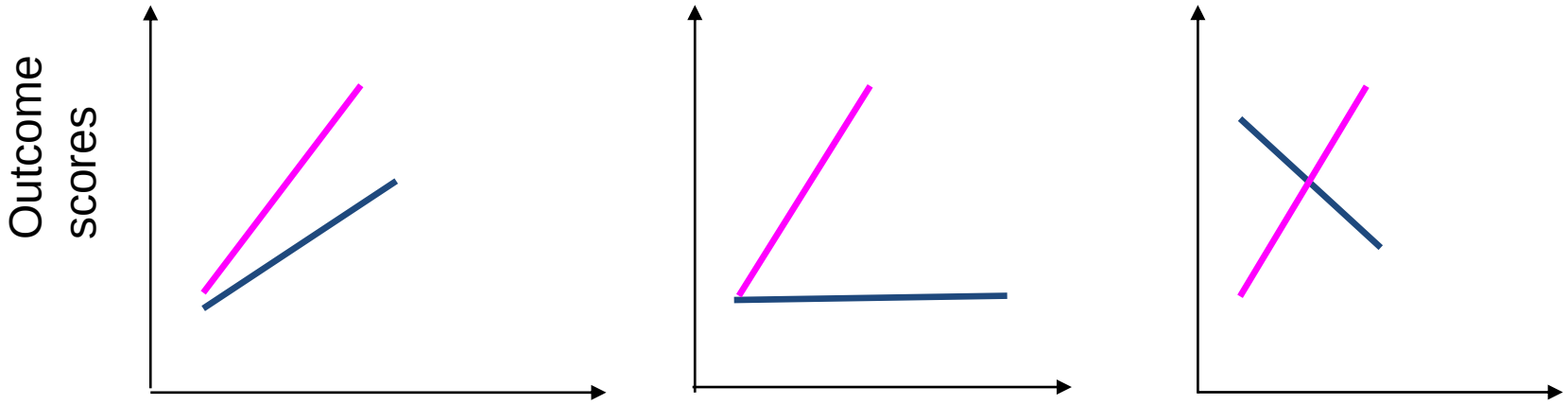

4.5 years

Reducing false positives

- We have many measures, are looking at complex interactions, and would always like greater statistical power (bigger sample). Mindless analysis followed by multiple-comparison correction would be very wasteful ! How do we try to reduce false positives?

- Trying to be as pre-specified as possible (e.g. MAOA only genotype examined so far, single Cpg methylation site)
- Use most powerful modelling methods for our study design but checked against analyses “close to the data”
- Use a persisting outcome, not one picked from a series of measures
- Confirm specific finding not explained by confounders or “generic” psychopathology (‘p’ factor)
- Use other studies to replicate and help triangulate

Statistical Interactions



Definite main effect

Possible main effect

No main effect

Interaction/moderation

Sex Differences Overview

Males more than females

- Early onset (except schizophrenia)
- Externalizing
- Neuro-cognitive
- Persistent non-episodic

Females more than males,

- Onset after puberty
- Internalizing
- Affective
- Episodic

Main Possibilities

- Risks and mechanisms for males and females are the same, but males more exposed to risks for externalising in early childhood (e.g. neurocognitive), and females for internalising during adolescence (e.g. peer victimization)
- The risks for males and females are different operating via same mechanisms (e.g. low birth weight, adolescent depression)
- The risks for males and females are the same but operate via different mechanisms (e.g low birthweight, vagal reactivity, ODD)
- But that may be because they are associated with different phenotypes (e.g. headstrong, irritability)

The Sex Difference Hypothesis – Broadly!

In males

- Failure of inhibitory processes for disruptive behaviours/aggression. Low inhibition associated with low emotional, autonomic or hormonal reactivity, and low social awareness - interactive risk with child maltreatment
- Impaired neurocognitive abilities

In females

- Increased dysregulated negative emotionality. Associated with emotional, autonomic or hormonal reactivity, or increased social awareness – interactive risk with child maltreatment

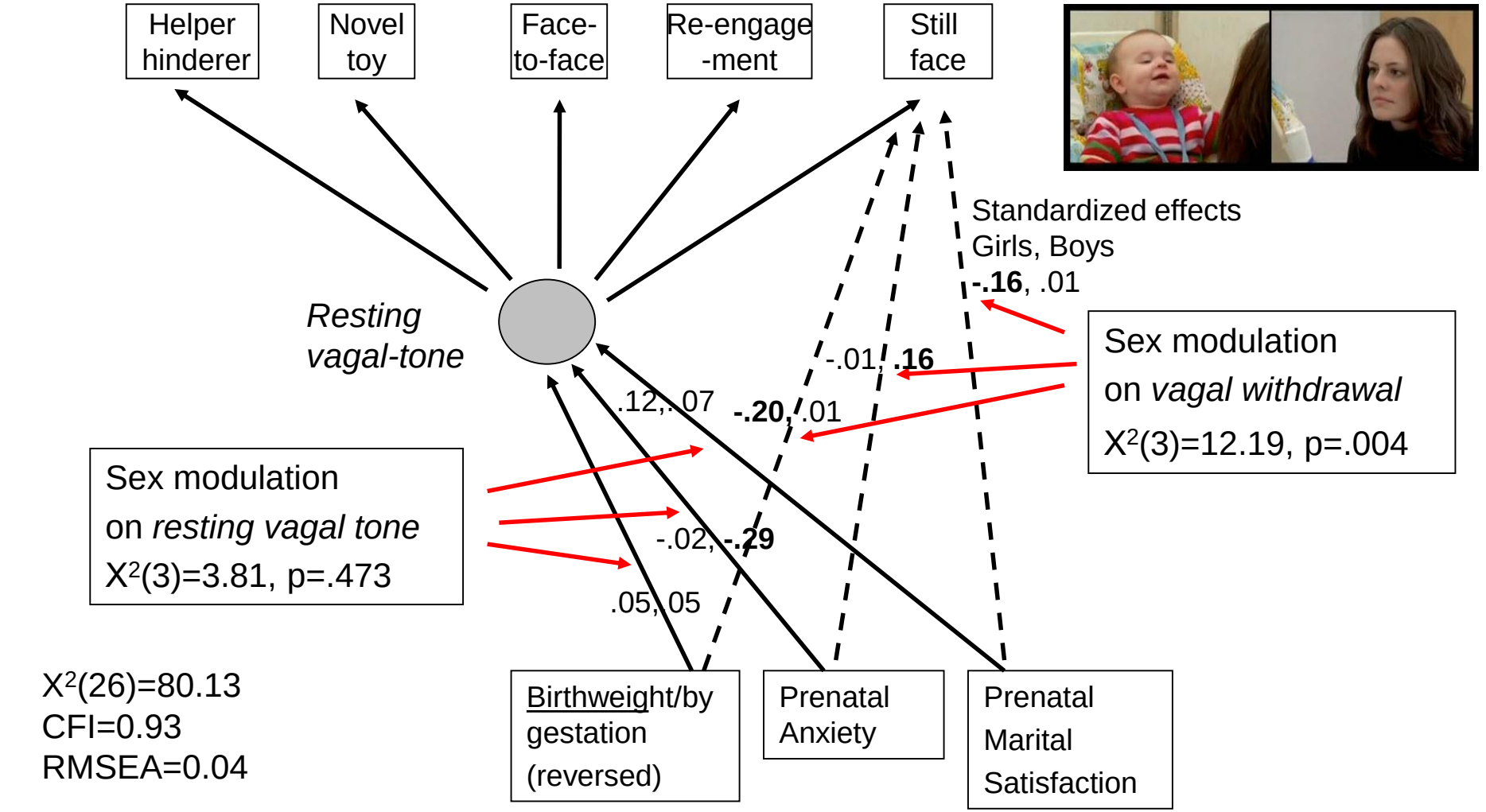
Vagal Reactivity in the Still Face at 7 Months

Effects on proximal physiology: Heart-rate variability (RSA)

Development and Psychopathology, page 1 of 10.
© Cambridge University Press 2014
doi:10.1017/S0954579414000194

Evidence for sex differences in fetal programming of physiological stress reactivity in infancy

FLORIN TIBU,[a] JONATHAN HILL,[a] HELEN SHARP,[b] KATE MARSHALL,[a] VIVETTE GLOVER,[c] AND ANDREW PICKLES[d]
[a]*University of Manchester;* [b]*University of Liverpool;* [c]*Imperial College London; and* [d]*King's College London*



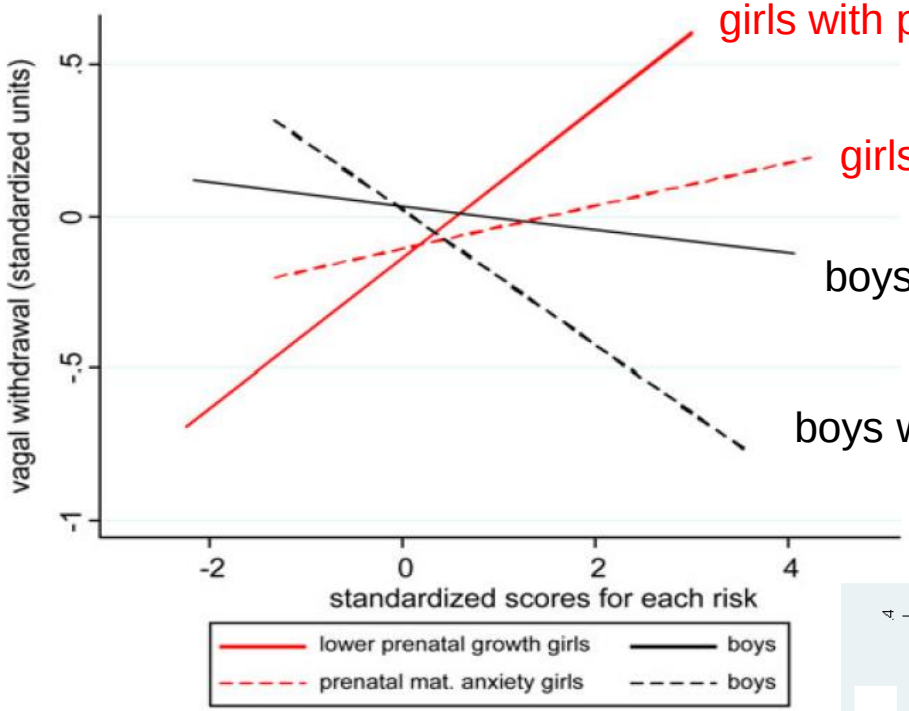
Effects on proximal physiology: Heart-rate variability (RSA)

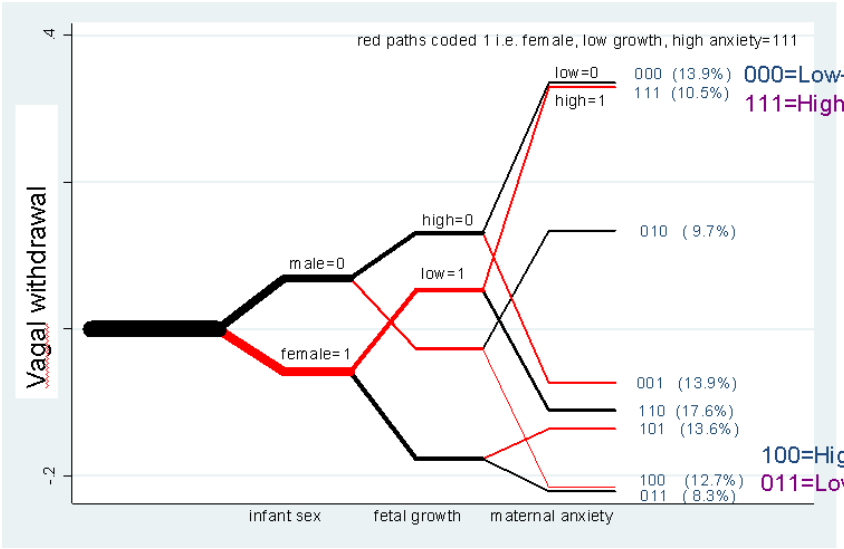
girls with poorer prenatal growth

girls with mums with prenatal anxiety

boys with poorer prenatal growth

boys with mums with prenatal anxiety



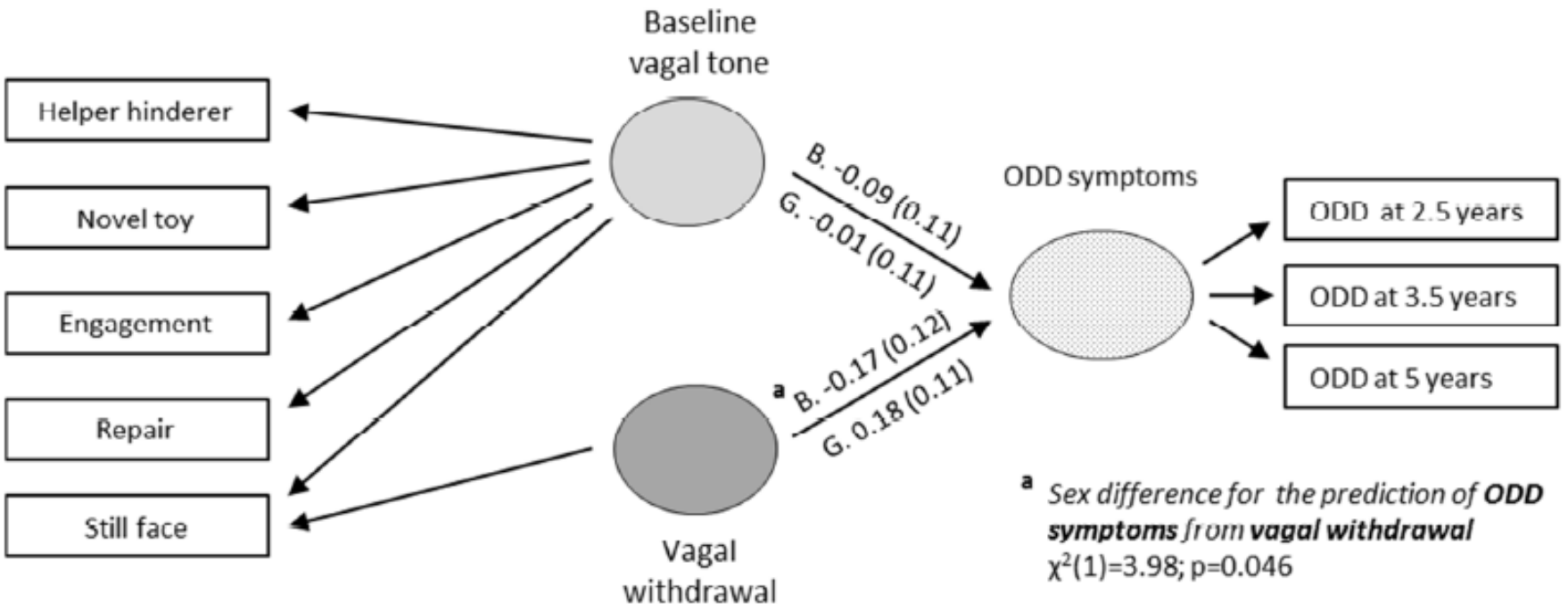


Consequences of altered early physiological reaction

The Journal of Child Psychology and Psychiatry
Journal of Child Psychology and Psychiatry 58:9 (2017), pp 988–997 doi:10.1111/jcpp.12750

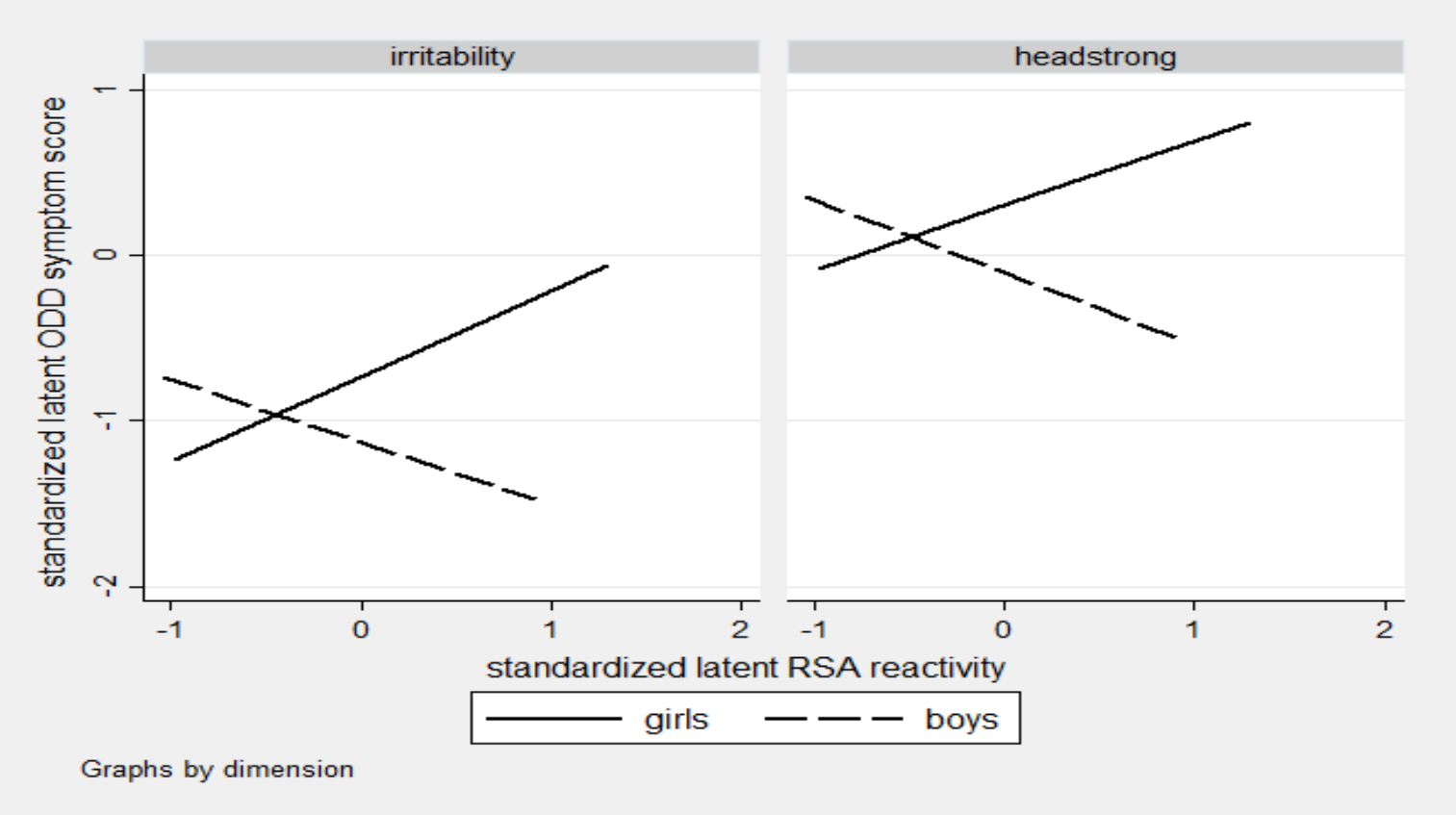
Sex differences in the associations between vagal reactivity and oppositional defiant disorder symptoms

Pablo Vidal-Ribas,[1] Andrew Pickles,[2] Florin Tibu,[3] Helen Sharp,[4] and Jonathan Hill[5]



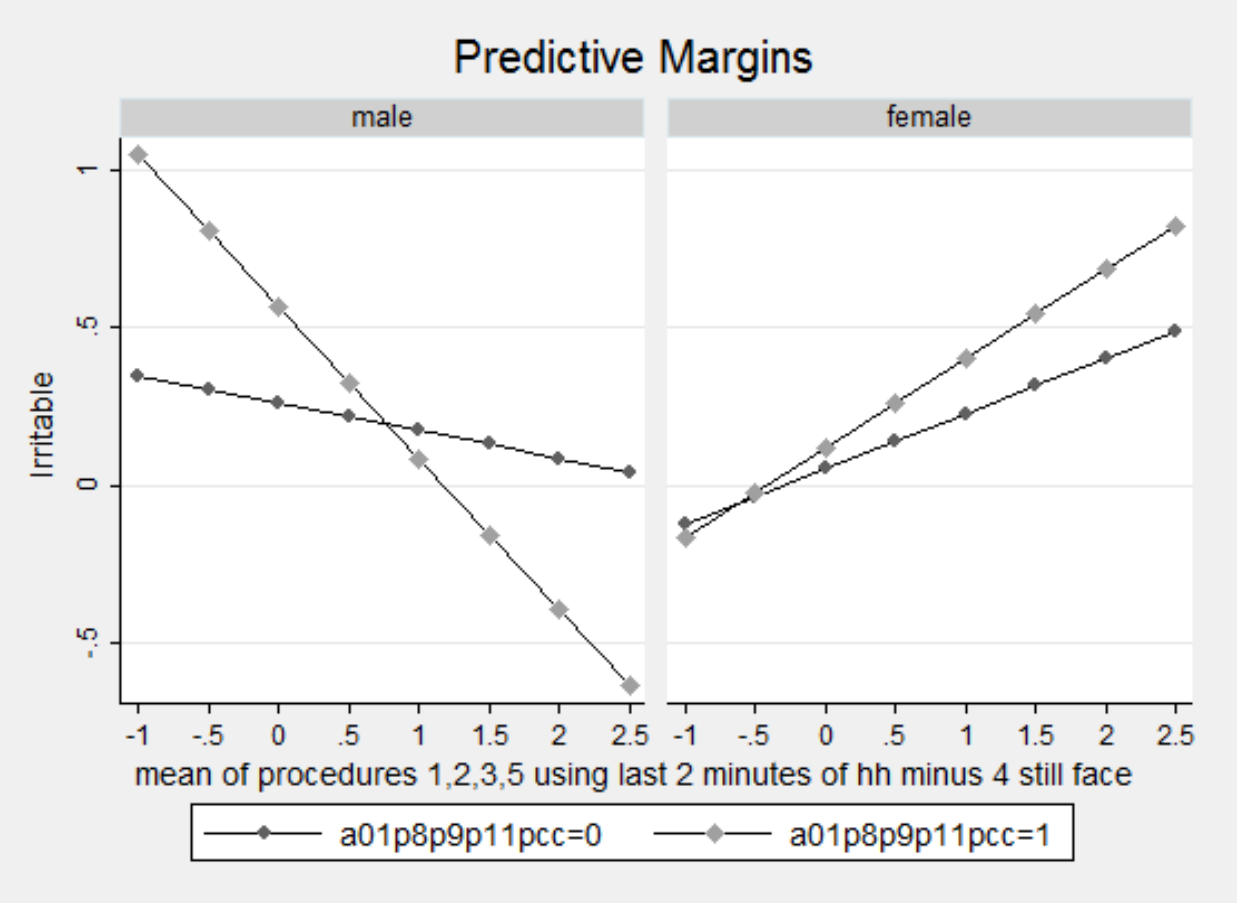
Increases later ODD symptoms in girls and decreases in boys

Partner Violence, Vagal Reactivity, ODD Symptoms in Boys and Girls from 2.5 – 5.0 Years



Exposure to partner violence associated with increasing irritability in the presence of LOW vagal reactivity in boys, but HIGH vagal reactivity in girls, interaction p = .015

Partner Violence, Vagal Reactivity, ODD Symptoms in Boys and Girls at Age 7 Years

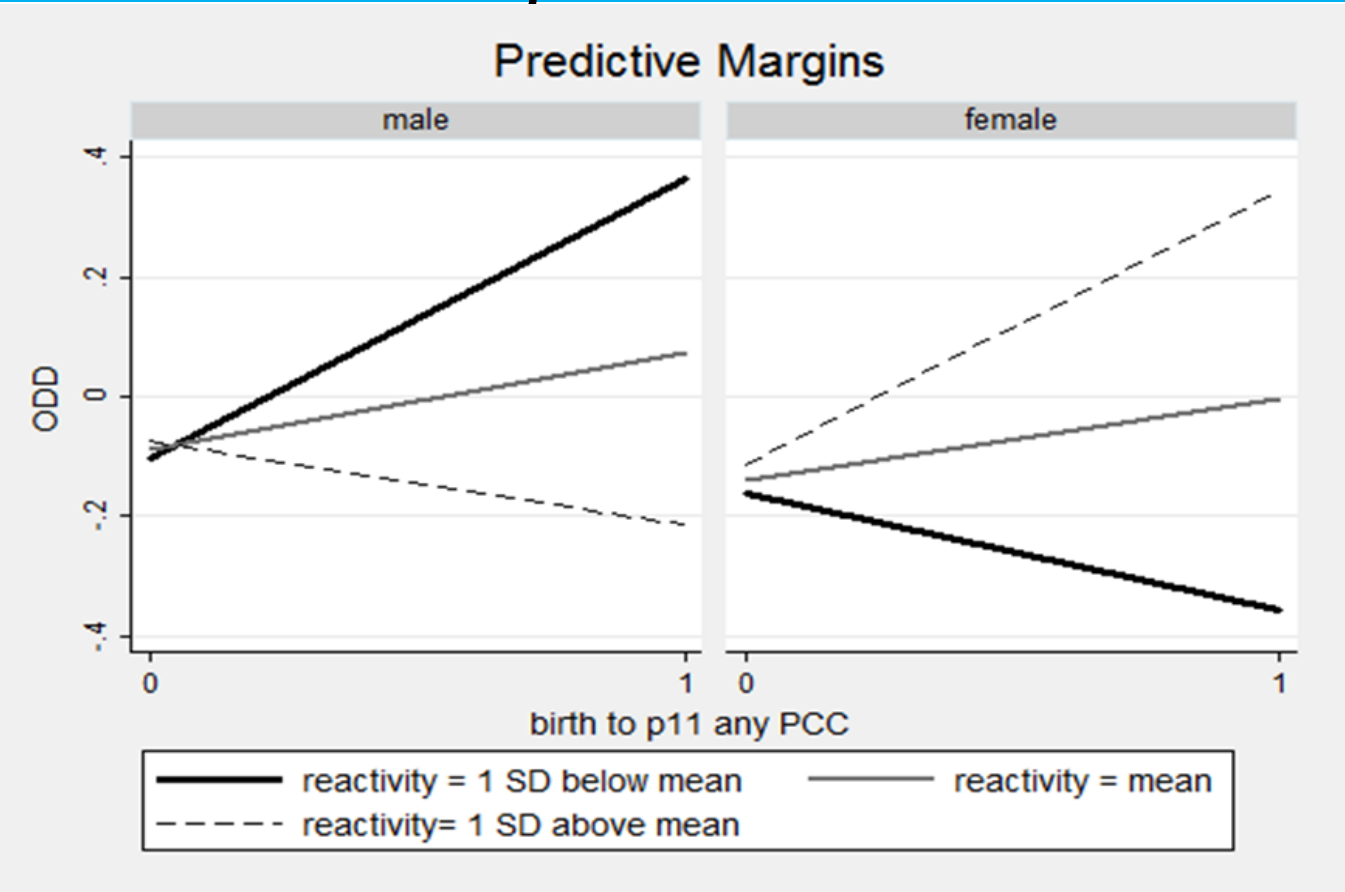


Exposure to partner violence associated with increasing irritability in the presence of LOW vagal reactivity in boys, but HIGH vagal reactivity in girls, interaction p = .006

Cortisol Reactivity

- Age 5 years
- Seven and a half minute recording of a conversation between two adults comprised 30 seconds chatting about benign topics, 2 minutes disagreement, 2 minutes intense argument, 2 minutes unresolved anger and 1 minute resolution
- Saliva for cortisol, two baselines separated by 20 minutes, one post-stress 20 minutes later

Exposure to Partner Violence, Cortisol Reactivity, ODD Symptoms in Boys and Girls at Age 7 Years



Exposure to partner violence associated with increasing ODD in the presence of LOW cortisol reactivity in boys, but HIGH cortisol reactivity in girls, interaction p = .015

Fetal Origins – The Vulnerable Male

- Under favourable conditions producing males is better – fit males compete more successfully (Trivers & Willard,1973)
- Under unfavourable conditions producing females is better – unfit males do not reproduce
- Animal and human evidence that producing males is more costly
- Therefore males are more vulnerable to prenatal insults and readily culled and females have more adaptive mechanisms

Fetal Origins – The Adaptive Female

- Preterm males have poorer survival than females
- Placentas of male preterm infants show more inflammation
- Preterm males have lower cardiovascular stability
- Synthetic steroid, betamethasone improves outcomes for preterm births, more in females than males
- **Greater cortisol reactivity in female foetuses and hence better cardiovascular stability in infants**

Sex differences in stress and HPA Axis

- In animal studies prenatal stress increases anxious and depressed type behaviours in female offspring, reduces in males – abolished by adrenalectomy (Zagron and Weinstock 2006).
- Hypothalamic CRH mRNA levels significantly increased by prenatal stress in females, but decreased in male rats (Garcia-Caceres et al, 2010)
- Increased CRH gene expression in amydgala in prenatally stressed female rats but not males (Zohar & Weinstock, 2011)
- Sex differences at the synapse! (Bangasser et al 2010)

Prenatal risk, HPA and psychopathology – sex Differences

- Prenatal anxiety predicts adolescent depression mediated via HPA axis changes – in girls only (Van Den Bergh et al 2008), may depend on timing (de Bruijn et al 2009)
- Low birthweight predicts adolescent depression - in girls only (Costello et al 2007, Van Lieshout et al 2010)
- Shared risk for cardiovascular disease and depression greater in females than males (Goldstein et al 2014)

Are these HPA axis mediated psychopathologies a function of the adaptive female fetus?

Pre and post-natal influences

- Fetal programming thought to be mediated via decreased expression of GR gene, elevated corticosterones and CRF with multiple endocrine, autonomic, behavioural effects
- Lick and groom effect in rodents mediated via increased GR gene expression
- If maternal stroking affects gene expression it should reverse effects of prenatal stress

Is this hypothesised HPA axis mediated mechanism specific to females?

Maternal Stroking

At 5 weeks and 9 weeks postnatal: four five-category items on how frequently mothers stroked their babies face, arms & legs, back and tummy

	Never	Rarely	Sometimes	Often	A lot
	%	%	%	%	%
I stroke my baby's tummy	1	6	33	35	25
I stroke my baby's back	1	10	27	35	27
I stroke my baby's face	0	2	19	43	36
I stroke my baby's arms and legs	1	6	33	34	26

In Principal Components Analysis, three factors:
Stroking
Holding
Affection
No associations between self-report stroking at 9 weeks and observed sensitivity at 29 weeks

Sharp et al (2012) PLOS One 10 (7) e45446

Weaver, (2004). Epigenetic programming by maternal behavior. Nature Neuroscience, 7, 847-854.

WCHADS Study

Sharp H et al. (2012) PLoS One

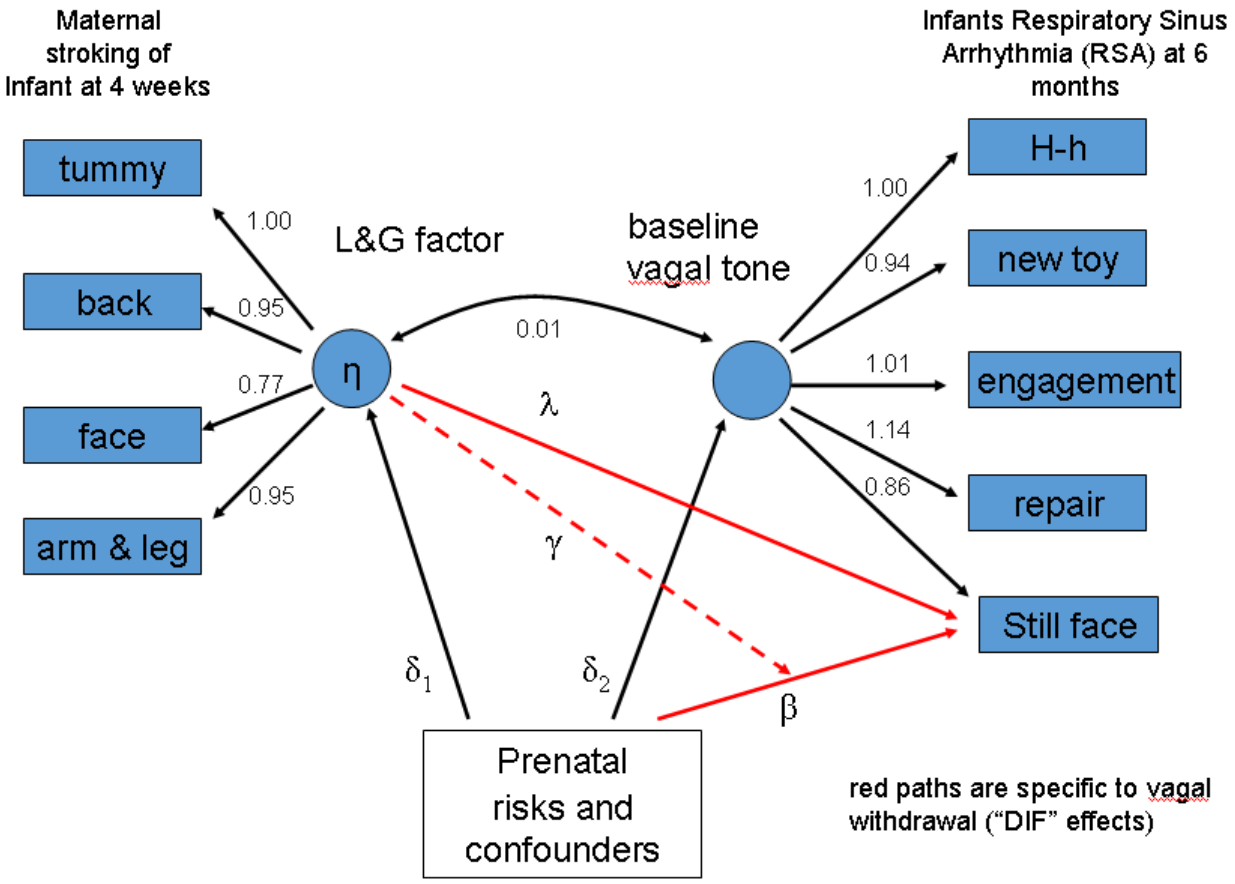
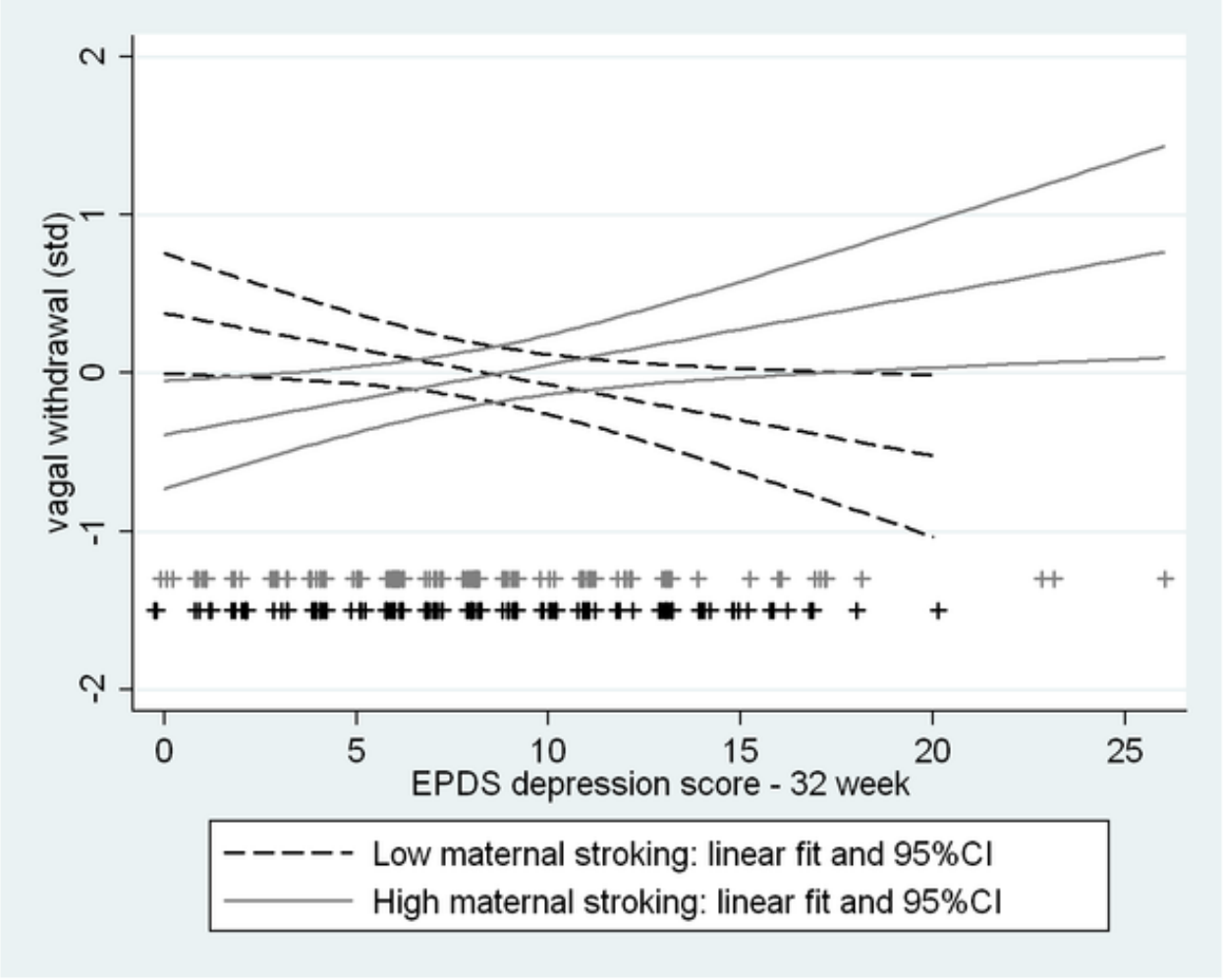
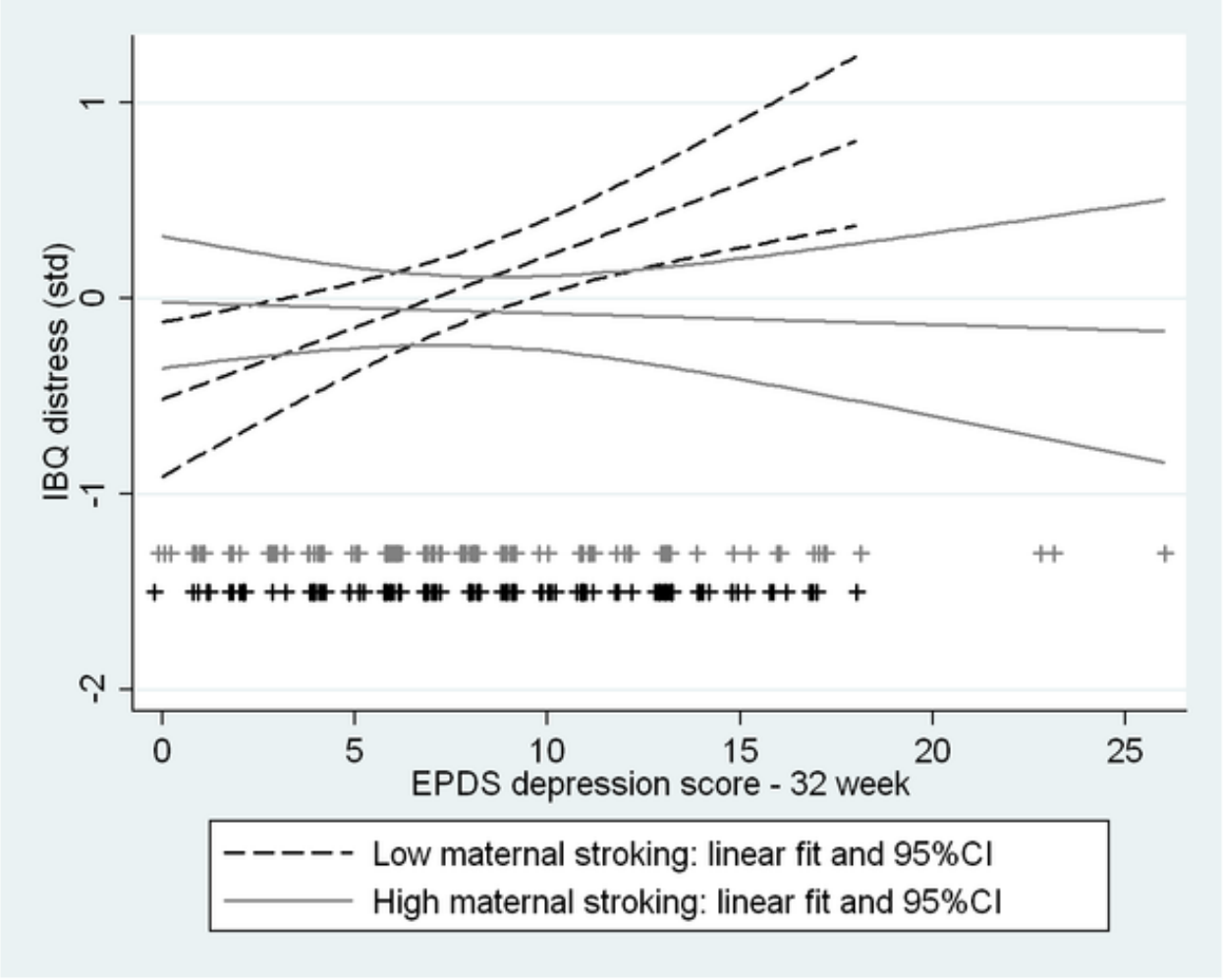


Figure 4. Interaction between maternal stroking and prenatal depression on infant vagal withdrawal.



Sharp H, Pickles A, Meaney M, Marshall K, Tibu F, et al. (2012) Frequency of Infant Stroking Reported by Mothers Moderates the Effect of Prenatal Depression on Infant Behavioural and Physiological Outcomes. PLOS ONE 7(10): e45446. https://doi.org/10.1371/journal.pone.0045446
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0045446

Figure 5. Interaction between maternal stroking and prenatal depression on infant distress to limitations.



Sharp H, Pickles A, Meaney M, Marshall K, Tibu F, et al. (2012) Frequency of Infant Stroking Reported by Mothers Moderates the Effect of Prenatal Depression on Infant Behavioural and Physiological Outcomes. PLOS ONE 7(10): e45446. https://doi.org/10.1371/journal.pone.0045446
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0045446

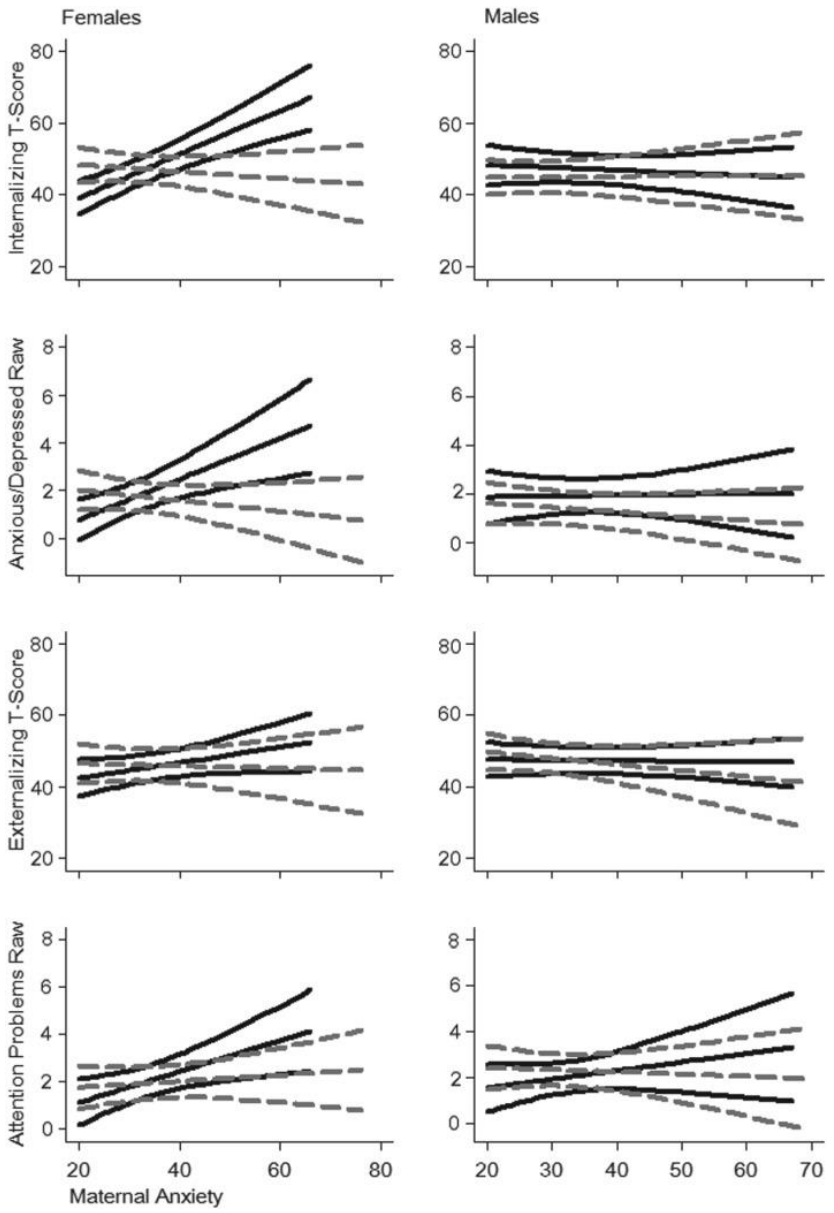
Psychological Medicine (2015), **45**, 269–283. © Cambridge University Press 2014
doi:10.1017/S0033291714001342

ORIGINAL ARTICLE

Maternal antenatal anxiety, postnatal stroking and emotional problems in children: outcomes predicted from pre- and postnatal programming hypotheses

H. Sharp[1], J. Hill[2]*, J. Hellier[3] and A. Pickles[3]

[1] *Institute of Psychology, Health and Society, University of Liverpool, Liverpool, UK*
[2] *Institute of Brain, Behaviour and Mental Health, University of Manchester, Manchester, UK*
[3] *Institute of Psychiatry, King's College London, London, UK*



Foetal origins hypothesis

- The foetus responds to the *in utero* environment with an adaptation to a future anticipated environment
- Low birth weight is an adaptation to future low nutrition environment – risk for diabetes and cardiovascular disease with high nutrition diets
- Matching hypothesis – poor outcomes for mismatch, e.g. low prenatal stress followed by high postnatal stress – **is this adaptive mechanism in some instances specific to females?**

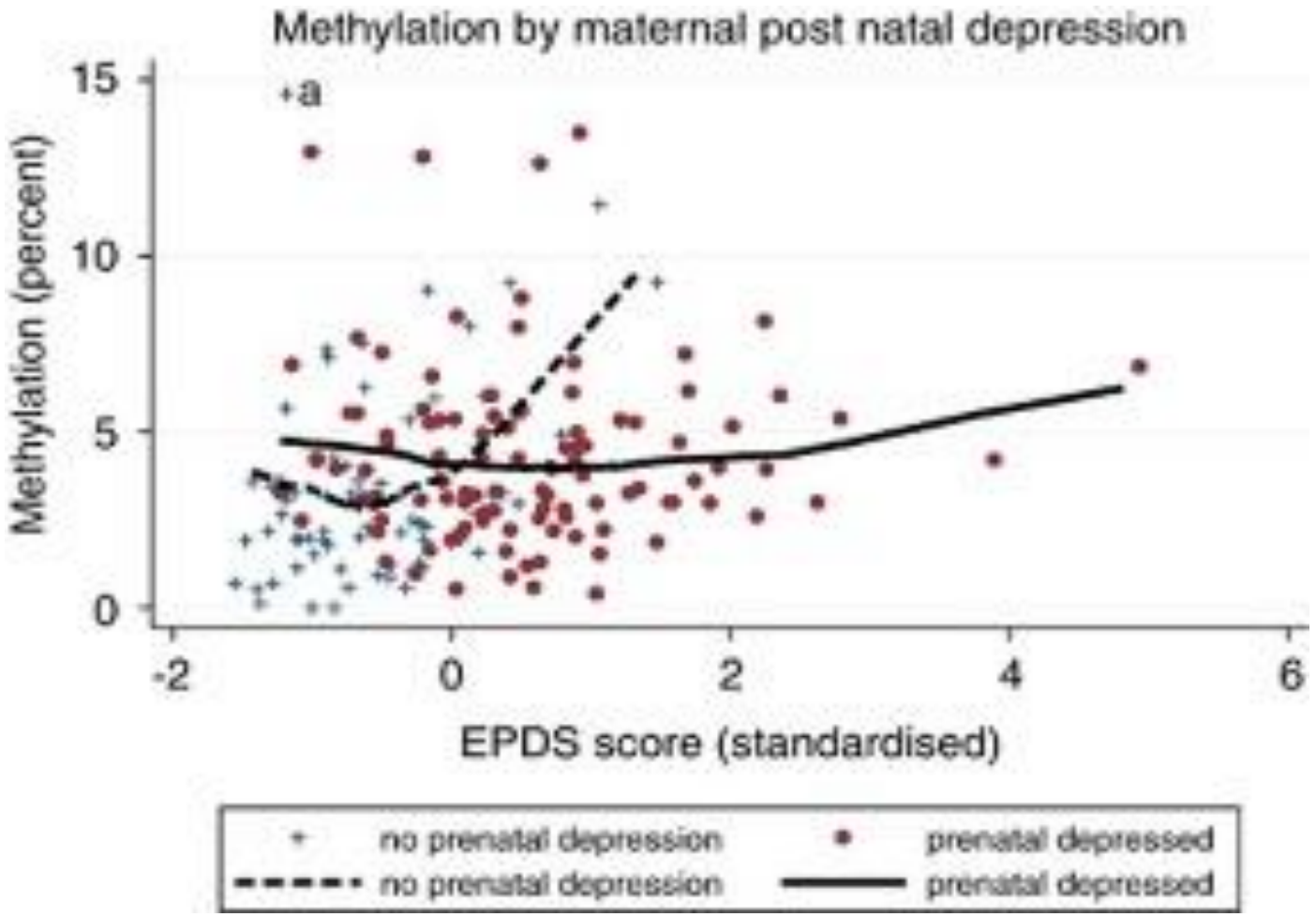
GR Gene Methylation

- Infant saliva at 14 months
- Percentage methylation at region 1F of the NR3C1 gene - gene expression regulatory region
- One CpG site examined based on previous studies
- Palma-Gudiel et al (2015) identify this site in meta - analysis

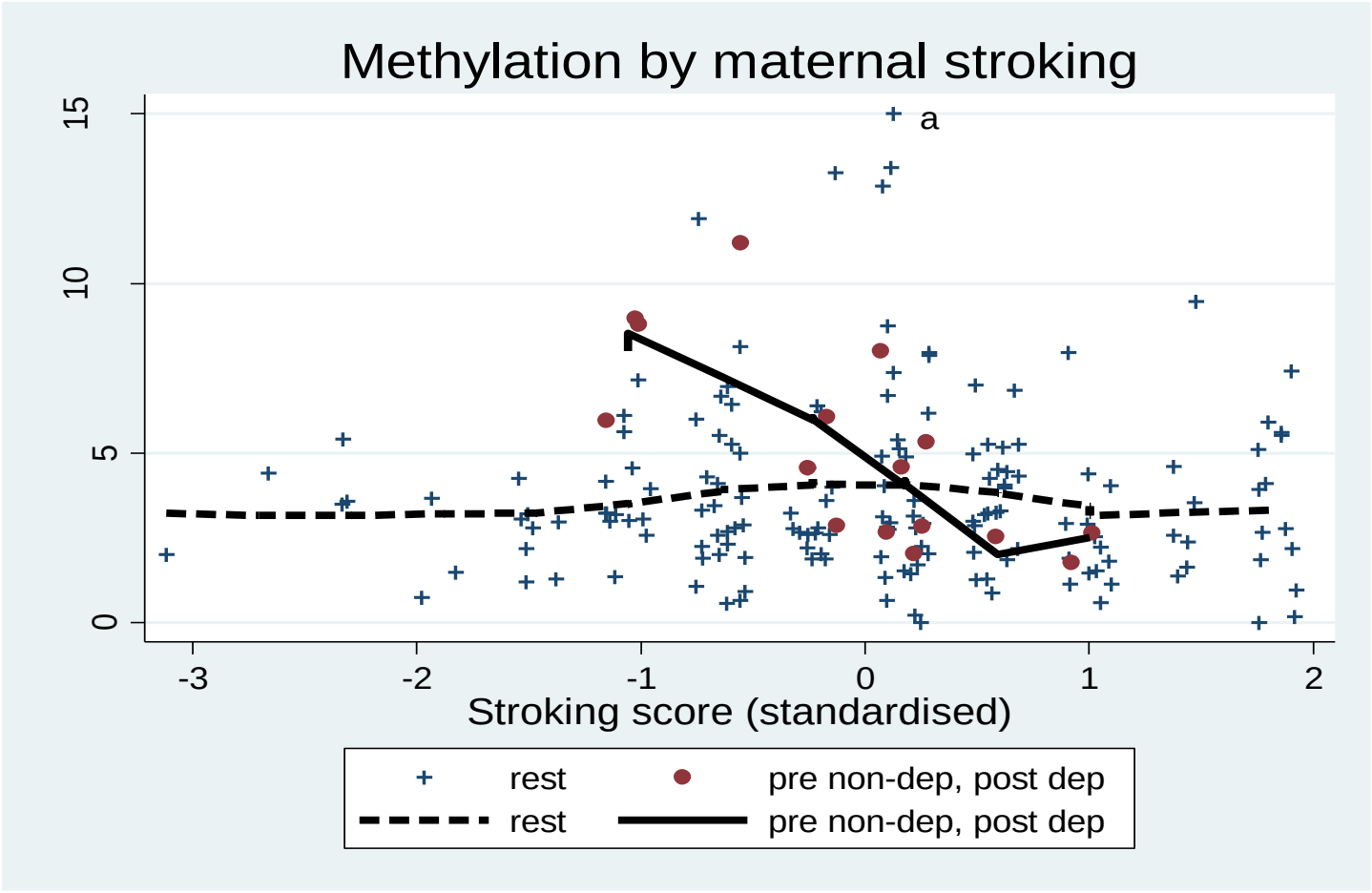
GR Gene, NR3C1 1-F Promoter Methylation

- Peripheral tissue
- Heterogeneity of cell type
- Identification of CpG sites, shores or islands
- We only looked at one replicated CpG site, later identified in a meta-analysis (Palma-Gudiel et al 2015)
- Saliva from 181 infants at age 14 months
- Bisulphite treated, amplified, run on a Sequenom EpiTYPER system

Low prenatal followed by high postnatal depression predicts elevated *NR3C1* 1-F promoter methylation *(Murgatroyd et al Trans Psych 2015)*

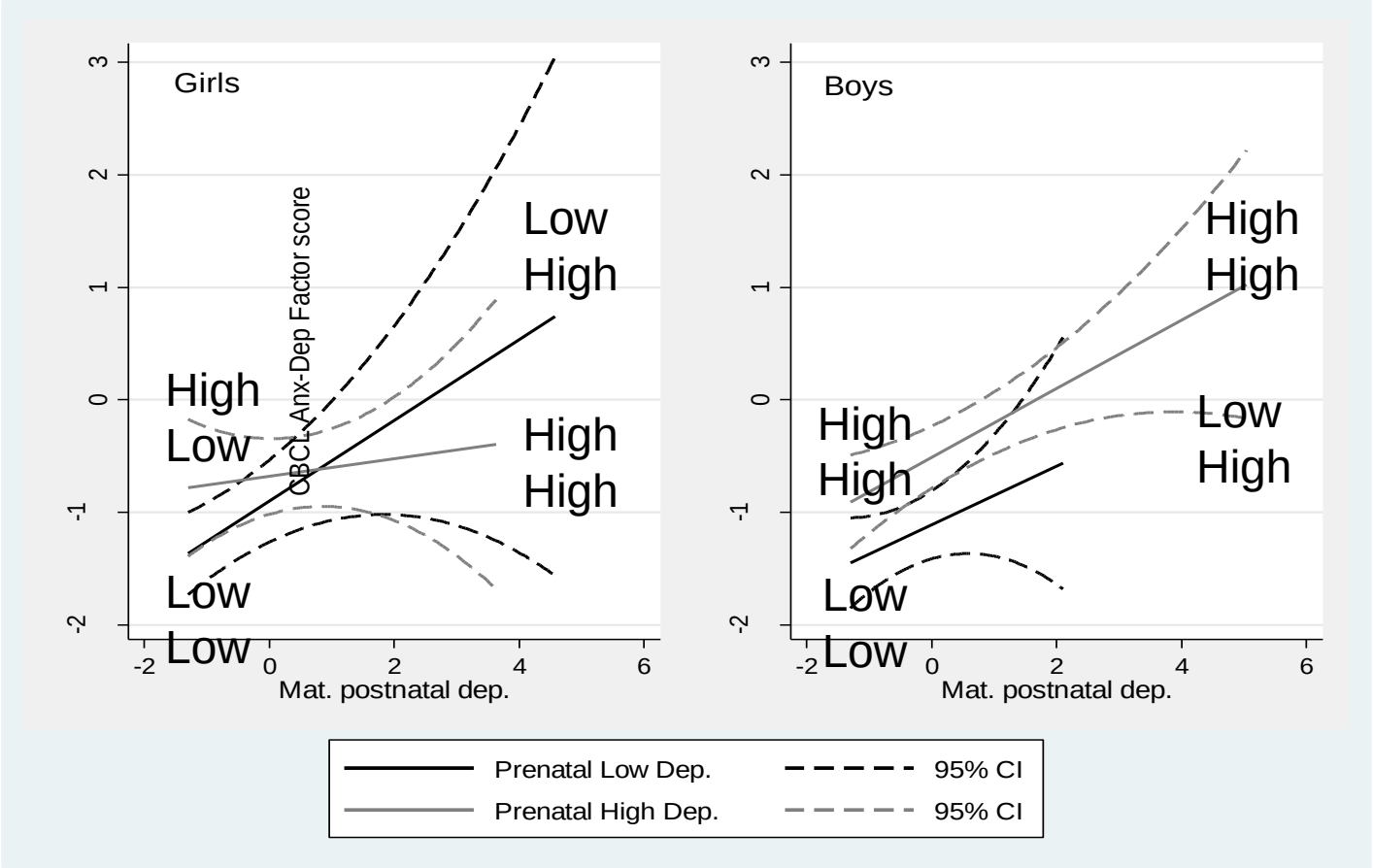


Maternal stroking reverses the prenatal-postnatal mismatch effect on methylation



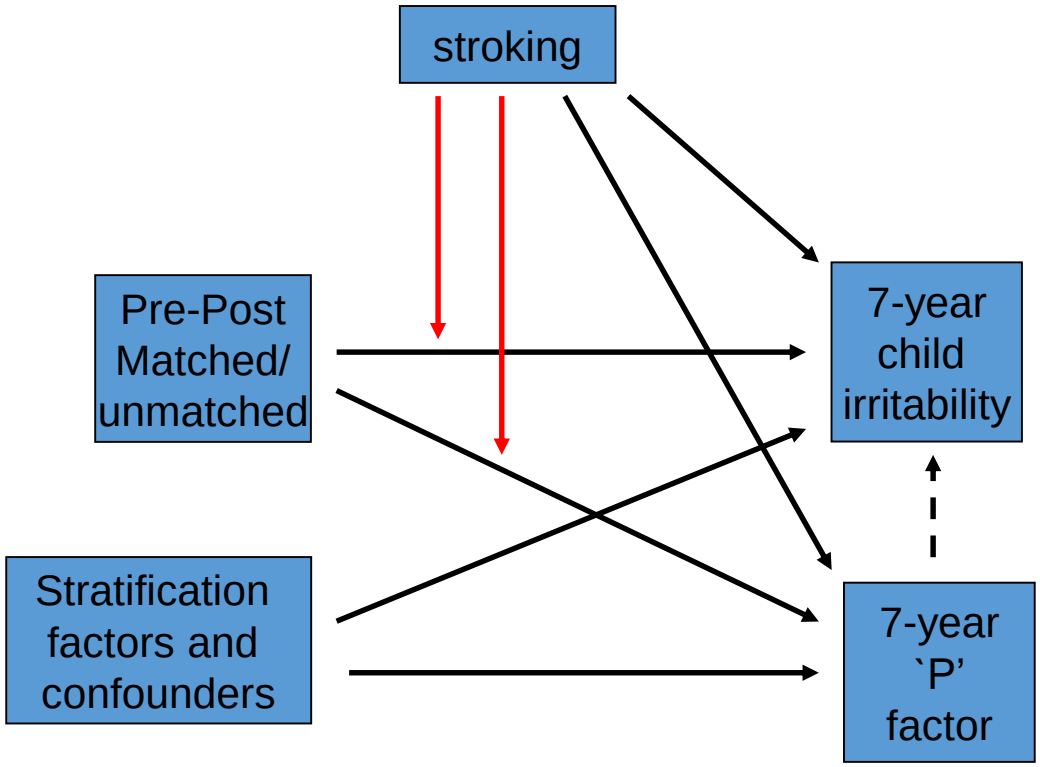
Mismatched pre-postnatal depression by maternal stroking interaction, $p < .001$

Pre-postnatal depression, child anxious-depressed symptoms 2.5, 3.5, 5 years, sex differences

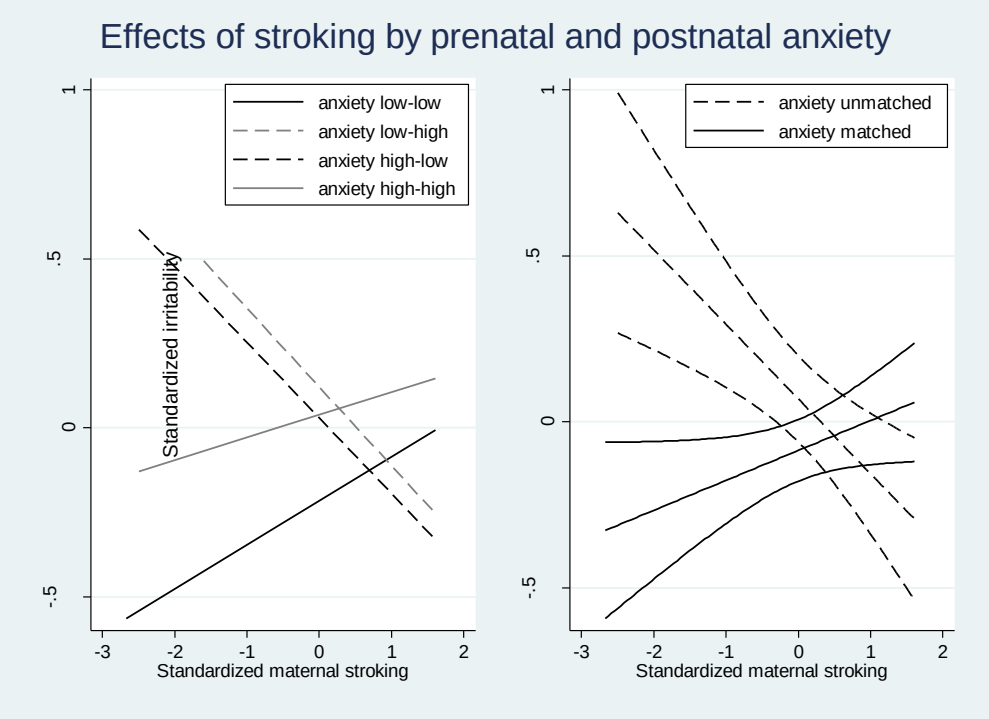


Elevated *NR3C1* methylation at 14 months mediates between pre-postnatal depression and child symptoms up to age 5 years

Feature selection: Matched and Unmatched Environments



Feature selection: Matched and Unmatched Environments



In separate linear regression models the variance of 7-year irritability explained by maternal stroking,

In girls: pre-post mismatched group 15.3% (p = <.001)
pre-post matched group 1.7% (p=.041)

In boys: pre-post mismatched group 0.2% (p=.639)
pre-post matched group 0.0% (p=.558)

Hypothesis for sex differences and prenatal and postnatal effects

- Males are selected for competitive reproductive fitness
- Male births are favoured when maternal conditions are good, and males vulnerable when they are bad
- Prenatal and postnatal risks are additive
- Male-typical disorders arise from lack of inhibition of evolved behaviours or deficits, lack of emotionality and social insensitivity
- Females are selected for protection of young
- Females births are favoured when maternal conditions are poor, and hence have greater adaptive capabilities
- Prenatal and postnatal risks are interactive
- Female-typical disorders arise from over inhibition or arousal, over emotionality and heightened social sensitivity

Support vs Falsification

- Selected findings with sex differences, others not – e.g. some stroking
- All effects so far in the same direction – i.e. not examples where risk has been associated with increased reactivity in boys, nor increased reactivity in boys with symptoms
- Would such a finding challenge the hypothesis or enrich it
- Does the hypothesis predict processes without sex differences? Yes!
- What will constitute replication or failure to replicate?

Clinical Implications

- Most phenotypes – ‘Disorders’ are in doubt
- Many are probably heterogeneous
- Sex/gender may be one important source of heterogeneity
- These findings may be enough to prompt the question “to what extent are this boy’s problems characterised by limitations in inhibition or regulation of behaviours?”
- Vagal reactivity not sufficiently predictive for clinical use, but a trial for boys symptoms could be stratified by vagal reactivity – does the treatment work best for those with low reactivity?