Title: Prenatal-postnatal maternal anxiety mismatch, maternal stroking, child irritability and general psychopathology 'p' at age 7 years; findings from the Wirral Child Health and Development Study

Authors: Jonathan Hill^a, Andrew Pickles^b Nicola Wright^c, Helen Sharp^c

^a School of Psychology and Clinical Language Sciences, University of Reading, Earley Gate, Reading, RG6 6AL, UK;

^b Institute of Psychiatry, Psychology and Neuroscience, De Crespigny Park, London SE5 8AF, UK;

^c Department of Psychological Science, Institute of Psychology, Health and Society, Whelan Building, University of Liverpool, Brownlow Hill, Liverpool L69 3GB, UK

Running head: Maternal anxiety and stroking, child irritability

Abstract

Background

According to fetal origins hypotheses, mismatched prenatal-postnatal conditions will be associated with poor health outcomes. Based on previous findings from the Wirral Child Health and Development Study (WCHADS) that associations between prenatal anxiety and child anxious- depressed symptoms were modified by mothers' reports of infant stroking, we predicted similar effects following mismatched prenatal-postnatal maternal anxiety. Low stroking would be associated with poorer outcome. In view of associations between oppositional defiant disorder (ODD) irritability and adolescent depression, our models predicted irritability, controlling for general psychopathology 'p', and contrasted with headstrong, to test for specificity. Based on animal and human evidence we predicted that the effect would be seen only in girls.

Methods

Mothers in the WCHADS, a general population cohort recruited at 20 weeks pregnancy, provided self- reported anxiety during pregnancy, and at 9 weeks, 14 months and 3.5 years postpartum, frequency of infant stroking at 9 weeks. Mothers and teachers reported child symptoms at age 7 years. Irritability scores were available from 668 children, and SEM models with maximum-likelihood estimates made use of data from 887 participants.

Results

There was a three way interaction between prenatal and postnatal anxiety and maternal stroking. This arose because lower stroking at 9 weeks was associated with higher irritability at 7 years, only in the mismatched, low-high and high-low maternal anxiety groups. The effect was unchanged after accounting for associations with general psychopathology, 'p'. There was no effect on headstrong symptoms. Despite an overall effect on irritability in separate analyses this was confined to girls.

Conclusions

Postnatal modifications of prenatal effects of maternal anxiety were specific to child irritability, and seen only in girls. Given associations between child irritability and adolescent depression, the findings provide further indications of mechanisms for fetal and postnatal origins of affective disorders in adolescence and beyond.

Key Words:

Maternal anxiety: maternal stroking: prenatal-postnatal matching: oppositional defiant disorder: irritability: headstrong: general psychopathology

Abbreviations:

ODD: oppositional defiant disorder

ADHD: attention deficit and hyperactivity disorder

WCHADS: Wirral Child Health and Development Study

NR3C1: nuclear receptor subfamily 3, group C, member 1

GR: glucocorticoid receptor

HPA: hypothalamic–pituitary–adrenal

CFA: confirmatory factor analysis

CBCL: child behavior checklist

TRF: teacher report form

PICTS: parent infant caregiving touch scale

IMD: Index of Multiple Deprivation

Two contrasting ways of conceptualizing child and adolescent psychiatric disorders have gained ground over the past 20 years. From the first ‘splitter’ perspective current phenotypes are seen as too broad, with the risk that their heterogeneity will undermine efforts to uncover their origins. From the other, ‘lumper’ view, current phenotypes that apparently demarcate distinct disorders, are in fact different manifestations of a broad vulnerability for a general psychopathology ‘p’. Far from competing, these hypotheses have the potential to perform complementary functions in identifying causal mechanisms, by allowing us to partition mechanisms for narrower phenotypes from those for a general psychopathology. In this study we examine developmental pathways to child irritability, a subset of ODD symptoms, accounting both for the same pathways to p and for the association between irritability and p.

There is increasing evidence for distinct emotional dysregulation and disruptive behavior dimensions in ODD (Burke et al., 2014; Cavanagh, Quinn, Duncan, Graham & Balbuena, 2017). These two dimensions - named ‘irritability’ and ‘headstrong’ - predict different longitudinal outcomes (Stringaris & Goodman, 2009; Vidal-Ribas, Brotman, Valdivieso, Leibenluft, & Stringaris, 2016) with irritability associated with depression and headstrong with conduct problems and attention-deficit hyperactivity disorder (ADHD) (Stringaris & Goodman, 2009).

Long-term associations between indices of prenatal stress and child and adolescent emotional and behavioral problems have been extensively reported (O’Connor, Heron, Golding & Glover, 2003; O’Donnell, Glover, Barker, & O’Connor, 2014; Quarini et al., 2016). Little is known, about childhood mediators between prenatal stress and adolescent depression, however findings from a recent study suggest a role for childhood irritability. In a general population sample of 3,963 mother–child pairs there was a pathway linking prenatal maternal depressive symptoms, childhood irritability symptoms and adolescent depressive

symptoms (Whelan, Leibenluft, Stringaris & Barker, 2015). Childhood conduct problems by contrast, excluding irritability did not predict adolescent depression.

While studies finding different developmental pathways involving irritability and headstrong are increasingly persuasive, many childhood symptom clusters are commonly associated with other symptoms, and may simply be markers for a more general psychopathology, ‘p’ (Caspi et al., 2014). Modelling p and symptom clusters of interest jointly allows us to examine mechanisms for general and specific psychopathology.

Mainly on the basis of animal studies, prenatal (‘fetal programming’) effects are thought to arise from hypothalamic–pituitary–adrenal (HPA) axis dysregulation associated with reduced glucocorticoid receptor (GR) expression (O’Connor et al., 2005; Meaney, 2010). In rodents opposite effects of postnatal maternal behaviors are seen, whereby maternal ‘licking and grooming’ (LG) increase GR expression via promoter region demethylation, improving HPA axis regulation, and reducing anxiety behaviors (Lemaire, Lamarque, Le Moal, Piazza & Abrous, 2006; Del Cerro et al., 2010). In animals the postnatal effects are caused by tactile stimulation leading us to hypothesize that similar effects might arise in humans from the effect of maternal stroking. Based on self-reports at 5 and 9 weeks, we found that maternal stroking modifies associations between prenatal anxiety or depression with infant temperament and vagal reactivity at age 29 weeks (Sharp et al., 2012), child internalizing symptoms at age 2.5 years (Sharp, Hill, Hellier, & Pickles, 2015), and child internalizing and externalizing scores at age 3.5 years (Pickles, Sharp, Hellier, & Hill, 2016). The direction of effect of maternal stroking was the same on each occasion, such that the effect of the prenatal risk on child outcomes was markedly reduced for mothers who reported high levels of stroking.

The fetal origins hypothesis, first proposed to account for associations between low birth weight and obesity, cardiovascular disease, and Type II diabetes in middle and old age

(Barker, 2007) not only hypothesises that fetal conditions affect later outcomes, but that the effect arises because low birth weight is a fetal adaptation in anticipation of later food scarce environments. The adverse outcome arises where there is a mismatch between this adaptation and the high calorie diets, common in industrialized societies. The key is whether or not there is matching between prenatal and postnatal conditions. Far from being a mechanism specific to nutrition in humans, adaptations prior to birth that anticipate later environments are found throughout biology, possibly reflecting a pervasive and long conserved 'Predictive Adaptive Response' (PAR) mechanism (Bateson, Gluckman, & Hanson, 2014). The implication of this hypothesis applied to prenatal anxiety and depression, is that low levels will create vulnerability in the presence of later exposure to postnatal anxiety or depression, and that high levels will be protective, and *vice versa*. Based on the evidence that these effects are likely to be mediated by HPA axis variation, we examined the PAR match-mismatch hypothesis in the Wirral Child Health and Development Study and showed that the combination of low prenatal depression and high postnatal depression, as evidenced in a statistical interaction, was associated with elevated *NR3C1* 1-F promoter methylation, and that this effect was reversed by higher levels of maternal stroking (Murgatroyd, Quinn, Sharp, Pickles, & Hill, 2015).

Glucocorticoid mechanisms have also been implicated in fetal origins of infant negative emotionality, likely to be a precursor of child irritability (Whelan et al., 2015). Several studies have reported associations between maternal cortisol during pregnancy and infant negative emotionality (Davis et al., 2007; Baibazarova et al., 2013) although with some inconsistencies in the findings (e.g. Bergman, Glover, Sarkar, Abbott & O'Connor, 2010). It is therefore plausible to hypothesize that PAR match-mismatch mechanisms and maternal stroking will be implicated in childhood irritability.

Many associations between prenatal risks thought to implicate glucocorticoid mechanisms and adolescent depression, are seen in girls but not in boys (Costello, Worthman, Erkanli, & Angold, 2007; Quarini et al., 2016; van den Bergh, van Calster, Smits, van Huffel & Lagae, 2008; van Lieshout & Boylan, 2010). We have reported from two samples that higher maternal cortisol is associated with greater infant negative emotionality only in girls (Braithwaite et al., 2017; Braithwaite, Murphy, Ramchandi & Hill, 2017) that the prenatal-postnatal depression interaction is associated with child anxious-depressed symptoms only in girls, and that *NR3C1* 1-F promoter methylation mediates this association, in girls but not in boys (Hill et al., Under Review). Modification by postnatal maternal stroking of prenatal effects on child anxious-depressed symptoms may also be confined to girls (Sharp et al., 2015).

The aim of this study was to examine prenatal and postnatal risks for child irritability at age 7 years. First we hypothesized that elevated irritability would be predicted by a three way interaction between prenatal and postnatal anxiety and maternal stroking, arising from effects of mismatched prenatal and postnatal conditions in the absence of the beneficial effects of higher maternal stroking. Second we predicted that this effect would be seen for irritability and not for headstrong symptoms, and after accounting for an index of general psychopathology in the model. Third we predicted that these associations would be seen in girls but not in boys.

Method

Study design and sample

The participants were members of the Wirral Child Health and Development Study (WCHADS), a prospective epidemiological longitudinal study starting in pregnancy with follow-up over several assessment points during infancy and childhood. This uses a two-stage stratified design in which a consecutive general population sample (the ‘extensive’ sample) is used to generate a smaller ‘intensive’ sample stratified by psychosocial risk and both are followed in tandem. This enables intensive measurement to be employed efficiently with the stratified subsample, while weighting back to the extensive sample enables general population estimates to be derived. The analyses presented here focus on the larger extensive sample which was identified from consecutive first-time mothers who booked for antenatal care at 12 weeks gestation between 12/02/2007 and 29/10/2008. The booking clinic was administered by the Wirral University Teaching Hospital which was the sole provider of universal prenatal care on the Wirral Peninsula, a geographical area bounded on three sides by water. Socioeconomic conditions on the Wirral range between the deprived inner city and affluent suburbs, but with very low numbers from ethnic minorities. The study was introduced to the women at 12 weeks of pregnancy by clinic midwives who asked for their agreement to be approached by study research midwives when they attended for ultrasound scanning at 20 weeks gestation. Ethical approval for the study was granted by the Cheshire North and West Research Ethics Committee on three occasions for longitudinal data collection, on the 27th June 2006, reference number 05/Q1506/107, 7th June 2010, reference number, 10/H1010/4, and on 22nd December 2014, reference number, 14/NW/1484

and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. After obtaining written informed consent, the study midwives administered questionnaires, and informed consent was obtained again at later phases of the study.

Of those approached by study midwives, 68.4 % gave consent and completed the measures, yielding an extensive sample of 1233 mothers with surviving singleton babies. Data were available on all 1233 from birth records and for anxiety measures at 20 weeks of pregnancy ('20 weeks gestation') and on 865 mothers for infant stroking at 9.3 ($SD = 3.6$) weeks ('9 weeks'). Postnatal maternal anxiety was reported by 859 mothers at 9 weeks, by 708 at 14.3 ($SD = 1.9$) months ('14 months'), and by 710 at 41.8 ($SD = 2.3$) months ('3.5 years'). Child outcomes were available by maternal report on 667 children and by teacher report on 627 children at 88.2 ($SD = 3.7$) ('7 years').

Measures

Maternal anxiety. Maternal anxiety was assessed at 20 weeks of pregnancy using the State Anxiety Scale (Spielberger, 1983), a widely used maternal self-report measure. Postnatal maternal anxiety was assessed using the same measure at 9 weeks, 14 months and 3.5 years.

Maternal stroking. Maternal stroking was assessed by self report using the Parent–Infant Caregiving Touch Scale (PICTS) at 9 weeks. The PICTS has 12 items covering a range of maternal touching and communication behaviors, that load on three factors of stroking, holding and affective communication (Koukounari, Pickles, Sharp, & Hill, 2015). Four stroking items assessed how often (1 = never, 2 = rarely, 3 = sometimes, 4 = often, 5 = a lot) mothers currently stroked their baby's face, back, tummy, arms, and legs. In this study scores

at 5 and 9 weeks were correlated $r = 0.58$, and the stroking factor showed substantial stability over the same period.

Child emotional and behavioral symptoms. Maternal reports of child symptoms were obtained at 7 years using the Child Behavior Checklist (CBCL), which has been extensively employed in studies of child and adolescent emotional and behavioral disorders (Achenbach & Rescorla, 2000). It has 99 items each scored 0 (not true), 1 (somewhat or sometimes true), and 2 (very true or often true). Teacher reports of child symptoms were obtained using the Teacher Report Form, also a widely used measure of child and adolescent symptomatology. Outcome variables were the highest of the maternal and teacher reports. Items that comprise the Total Problem Score were used to generate the estimate of the general psychopathology 'p' factor. ODD dimensions of irritability and headstrong symptoms were generated based on the items previously identified by confirmatory factor analyses (CFA) in adolescents and adults (Stringaris et al., 2012) and on CFA with data collected at ages 2.5, 3.5 and 5.0 years in this study (Vidal-Ribas, Pickles, Tibu, Sharp, & Hill, 2017).

Confounders. Demographic and biological risks known to be associated with prenatal stressors and child mental health disorders were included as potential confounders. Variables generated at 20 weeks of pregnancy included mother's age, her cohabiting/marital status, whether she had smoked during pregnancy, and whether or not she had stayed in full time education beyond age 18. Partner psychological abuse, which was the stratifier for the intensive sample, was assessed using a 20-item questionnaire covering humiliating, demeaning or threatening utterances in the partner relationship during pregnancy over the previous year (Moffitt et al., 1997). The variable included in the models was defined as the highest of the partner to participant and participant to partner scores at 20 weeks pregnancy. Socioeconomic status was measured using the revised English Index of Multiple Deprivation (IMD); (Noble et al., 2004) based on data collected from the UK Census in 2001.

Statistical analyses

To best estimate long term exposure during infancy we formed a factor from the 3 postnatal measurements of maternal anxiety that had been collected from the full cohort. Figure 1 shows the form of a series of structural equation models (SEM) that were fitted in Stata 14 to examine irritability and headstrong at age 7 years, each log-transformed to minimize skew. We used the program gllamm for model fitting (www.gllamm.org and Rabe-Hesketh, Skrondal & Pickles, 2002), as this allowed us to fit all the effects shown in the Figure corresponding to main effects from risk factors, stratifiers, and confounders (black), potential mediation of effects via the general psychopathology 'p' (thick blue) and interaction effects involving a latent variable (red) that are not easily fitted in other SEM programs.

We began by examining the estimated effects of 9-week maternal infant stroking as modifying the impact of the two-way interaction between maternal prenatal anxiety and the postnatal anxiety factor. The first model considered child irritability as the outcome and the second model considered child headstrong behavior as the outcome, with neither of these models including the estimate of general psychopathology assessed using CBCL/TRF total problem scores. Estimated by using full maximum-likelihood these models made use of data from 887 participants, including some with incomplete observations, under the assumption of data missing at random. This assumption was made more plausible by the inclusion of covariates thought to be associated with sample attrition. These models also included the following potential confounders of the experience-behavior relationship: maternal age, smoking in pregnancy, education and marital status, and neighbourhood deprivation. They also included the stratifier, partner psychological abuse at 20 weeks pregnancy.

The third (shown in Figure 1) and fourth more extended models included the prediction of the highest of the parent and teacher total CBCL score ('p') and its effects on the specific target behaviors of irritability and headstrong symptoms. These models required the total

CBCL score to be included as a predictor, reducing the available sample size to 669 participants. Here again covariates for attrition were included.

The predicted effects of matched and mismatched prenatal and postnatal anxiety were examined using binary variables – high prenatal, low prenatal, high postnatal, low postnatal maternal anxiety - derived from median splits of the prenatal anxiety measure and the postnatal anxiety factor score. Matched groups were defined as either high prenatal-high postnatal or low prenatal-low postnatal anxiety, and mismatched groups as high prenatal-low postnatal or low prenatal-high postnatal maternal anxiety. The linear effects of maternal stroking in each of the 4 groups, and the pooled matched and mismatched groups were displayed with their corresponding regression Wald p -value for the interaction term.

Results

Summary statistics for the measures included in the SEM are shown in Table 1. Table 2 shows the estimated effects of primary interest from the SEM fitted to the whole sample accounting for the stratifier and confounders. There was a significant three way interaction of pre- and postnatal anxiety and stroking on the prediction of child irritability, but no main nor interaction effects for headstrong symptoms. The effects of adding the total CBCL/TRF score, as an estimate of ‘ p ’ to the models are shown in Table 3. The three way interaction predicting ‘ p ’ was non-significant, but there was a strong association (p 's<.001) between ‘ p ’ and both irritability and headstrong. This reduced the magnitude of the pre- and postnatal anxiety by stroking interaction effect by about 0.13 to 0.14 in both cases, but the effect on irritability remained substantial and significant ($p = .002$).

Next the role of matched and mismatched pre- and postnatal anxiety was examined in 4 groups created by combining the binary high vs low variables. Consistent with the strong continuity between prenatal and postnatal anxiety, the two matched groups (low – low, $N =$

294, high – high $N = 307$), were much larger than the mismatched groups (low – high, $N = 125$, high – low, $N = 161$). In the left-panel of Figure 2 it can be seen that in both mismatched groups there was a strong negative association between maternal stroking and child irritability, such that the highest irritability scores were predicted by maternal anxiety mismatches and low maternal stroking, but in the presence of high stroking irritability scores were comparable to those in the matched groups. By contrast there were some indications that stroking was associated with a modest increase in irritability symptoms in the matched groups. The right-hand panel shows the relationships when formed into just two groups of matched and unmatched environments which gave a highly significant simple interaction with maternal stroking ($p < .001$).

Possible sex differences in the observed effects were examined by running the models in girls and boys separately. Fitting the model to the sample of girls ($n = 451$) there was a significant 3-way interaction ($p = .002$), with a somewhat larger effect (coeff. = 0.641) than in the whole sample (coeff. = 0.533). Among the boys ($n = 436$), the interaction coefficient was substantially smaller and non-significant (0.269, $p = .321$). For headstrong symptoms, by contrast 3-way interactions for girls (coeff. = 0.250, $p = .187$) and for boys (coeff. = -.187, $p = .489$) were non-significant. In separate linear regression models, in girls, maternal stroking explained 15.3% of the variance in irritability scores ($p = < .001$) in the mismatched prenatal-postnatal anxiety groups, and there was a small effect in the opposite direction explaining 1.7% of the variance, in the matched groups ($p = .041$). In boys, by contrast, maternal stroking explained 0.2% of the variance in the mismatched groups ($p = .639$) and 0.0% of the variance in the matched groups ($p = .558$).

Discussion

Based on previous findings for *NR3C1* 1-F promoter methylation from the WCHADS we predicted that maternal stroking would modify the effect of prenatal-postnatal mismatching of maternal anxiety. Drawing on studies of prenatal risks for adolescent depression, and of continuities between prenatal risks and child irritability, and between child irritability and adolescent depression, we predicted that this effect would be seen in relation to childhood irritability, but not headstrong symptoms. Given that apparent associations with specific outcomes may be better explained by associations with a general psychopathology factor, we could not be confident of the hypothesized specificity without accounting for general psychopathology. Based on evidence from a wide range of animal and human studies we predicted that these effects would be confined to females.

There was a three way interaction between prenatal anxiety, postnatal anxiety, and maternal stroking, in the prediction of child irritability at age 7 years, assessed using the highest of maternal and teacher reports. In order to determine whether this interaction arose because maternal stroking modified the effects of prenatal-postnatal anxiety mismatching, we compared its effect in matched and mismatched groups. We found that increasing maternal stroking was associated with decreasing irritability symptoms only in the two mismatched groups, with the highest irritability symptoms among children of mothers with prenatal-postnatal mismatch who reported stroking their infants least frequently. This effect was seen for irritability and not headstrong symptoms, after accounting for confounders and was not explained by any more global effects on general psychopathology. It was evident in girls but not in boys.

The study provides further support for the operation of predictive adaptive response (PAR) mechanisms in humans, and is the first to demonstrate long term modification of prenatal and postnatal risks by early maternal stroking, and to show that these mechanisms

are specific to child irritability. The findings are consistent with recent evidence linking prenatal risks specifically to child irritability and not to headstrong symptoms, (Whelan et al., 2015) and based on evidence from the same study, may provide further indications of childhood mechanisms for adolescent, and ultimately adult, depression. Our large but limited sample size persuaded us not to test formally for a sex difference (a fourth-order interaction), but the estimates suggested that the effects were restricted to girls, consistent with previous findings from this study that the prenatal-postnatal mismatching and maternal stroking effects are sex dependent (Hill et al., 2017 under review), and with the considerable evidence that links prenatal risks and adolescent depression in females (Costello et al., 2007; Quarini et al., 2016;). The findings add to evidence from the Wirral Child Health and Development Study of the role of maternal stroking in modifying associations between prenatal risks and physiological, epigenetic and behavioral outcomes which we have reported at 29 weeks (Sharp et al., 2012), 14 months (Murgatroyd et al., 2015), 2.5 years (Sharp et al., 2015), and 3.5 years (Pickles et al., 2017).

Strengths of the study include that the analyses were informed by hypotheses for the biology of prenatal and postnatal matching, that they were based on repeated measurement of postnatal exposure to maternal anxiety, and that the outcome was assessed from both maternal and teacher reports. A limitation is that maternal stroking was based only on maternal self-report. In the future, demonstrating agreement with observational measures will also be relevant to establishing validity, although such observational measures are generally limited in studies of human development by restricted coverage over place and time, and so cannot straightforwardly be considered as ‘gold standard’. As in the case of temperament research in infancy, in the absence of an agreed ‘gold standard’, self-report and observational measures perform complementary functions (Rothbart, Chew & Gartstein, 2001) and further investigation of maternal stroking in infancy is likely to be approached

similarly. Although the rationale for investigating maternal stroking in this study was the animal evidence for epigenetic effects of tactile stimulation on HPA axis regulation, in humans tactile stimulation has many other effects. Characteristic patterns of prefrontal cortex and limbic activations have been shown in response to stroking with a pleasant stimulus, such as velvet, contrasted with a neutral or unpleasant stimulus, such as sandpaper (Gordon et al., 2013).

There are four main implications of findings that pre-postnatal mismatch maternal conditions predict poorer child outcomes. First they suggest that variations in maternal emotional symptoms confer risk in a more complex way than previously thought because they contribute to, or reflect, processes that are adaptive or maladaptive depending on prior and later experiences. Second they imply that early interventions may need to target not only mothers with elevated symptoms, but also those in pregnancy with few symptoms, but who may be at risk for onset postpartum, and also those whose prenatal symptoms improve following the birth of their child. Third, in the context of available evidence for fetal origins of adolescent and hence adult depression, and for child irritability as a key mediator, the findings have the potential to further illuminate and hence provide the basis for childhood prevention of later depression. Finally, the study highlights how joint consideration of narrow and broad symptom profiles, within a longitudinal design, and testing mechanism based hypotheses, can help clarify psychopathological phenotypes

Key points

- There is good evidence for long term effects of fetal conditions on emotional and behavioral outcomes
- This study indicates that these effects are modified by postnatal maternal mental health, and how often mothers stroke their babies
- The effects are specific to child irritability which provides an early indicator of risk for adolescent depression
- The effects are also specific to girls and so may be part of the mechanism for the greater incidence of adolescent depression in girls than in boys
- An important clinical implication is that the children of mothers who become anxious for the first time following the birth of their child, or who have been anxious in pregnancy and recover postnatally, may be at risk for later symptoms

Acknowledgements

We are very grateful to all participating families and to the research staff who contributed to this work. We also thank Wirral University Teaching Hospital NHS Foundation Trust who supported initial recruitment and to Cheshire and Wirral Partnership NHS Foundation Trust and Wirral Community NHS Foundation Trust for their current support and the NIHR Biomedical Research Centre for Mental Health at the South London and Maudsley NHS Foundation Trust and King's College London. We would also like to extend our thanks to all the staff involved in the WCHADS study.

This study was funded by grants from the UK Medical Research Council (G0400577, G0900654, MR/L022257/1).

Correspondence

Corresponding author: Jonathan Hill, School for Psychology and Clinical Language Sciences, University of Reading, Earley Gate, Reading, RG6 6AL, UK.

Email: j.hill@reading.ac.uk; Phone: 44 118 3785823

References

- Achenbach, T. M., & Rescorla, L. A. (2000). *Manual for the ASEBA preschool forms & profiles: An integrated system of multi-informant assessment; Child behavior checklist for ages 1 1/2-5; Language development survey; Caregiver-teacher report form*: University of Vermont.
- Baibazarova, E., van de Beek, C., Cohen-Kettenis, P. T., Buitelaar, J., Shelton, K. H., & van Goozen, S. H. (2013). Influence of prenatal maternal stress, maternal plasma cortisol and cortisol in the amniotic fluid on birth outcomes and child temperament at 3 months. *Psychoneuroendocrinology*, 38(6), 907-915.
- Barker, D.J. (2007). The origins of the developmental origins theory. *Journal of International Medicine*, 261(5):412-417.
- Bateson, P., Gluckman, P., & Hanson M. (2014). The biology of developmental plasticity and the Predictive Adaptive Response hypothesis. *The Journal of Physiology*, 592(Pt 11):2357-2368.
- Bergman, K., Glover, V., Sarkar, P., Abbott, D. H., & O'Connor, T. G. (2010). In utero cortisol and testosterone exposure and fear reactivity in infancy. *Hormones and Behavior*, 57(3), 306-312.
- Braithwaite, E.C., Murphy, S.E., Ramchandani, P.G., & Hill, J. (2017). Associations between biological markers of prenatal stress and infant negative emotionality are specific to sex. *Psychoneuroendocrinology*, 86, 1-7.
- Braithwaite, E. C., Pickles, A., Sharp, H., Glover, V., O'Donnell, K. J., Tibu, F., & Hill, J. (2017). Maternal prenatal cortisol predicts infant negative emotionality in a sex-dependent manner. *Physiology and Behavior*, 175, 31-36.
- Burke, J. D., Boylan, K., Rowe, R., Duku, E., Stepp, S. D., Hipwell, A. E., & Waldman, I. D. (2014). Identifying the irritability dimension of ODD: application of a modified bifactor

- model across five large community samples of children. *Journal of Abnormal Psychology*, 123(4), 841-851.
- Caspi, A., Houts, R. M., Belsky, D. W., Goldman-Mellor, S. J., Harrington, H., Israel, S., Meier, M., Ramrakha S., Shalev I., Poulton, R., & Moffitt, T. (2014). The p factor: one general psychopathology factor in the structure of psychiatric disorders? *Clinical Psychological Science*, 2(2), 119-137.
- Cavanagh, M., Quinn, D., Duncan, D., Graham, T., & Balbuena, L. (2017). Oppositional defiant disorder is better conceptualized as a disorder of emotional regulation. *Journal of Attention Disorders*, 21(5), 381-389.
- Costello, E. J., Worthman, C., Erkanli, A., & Angold, A. (2007). Prediction from low birth weight to female adolescent depression: a test of competing hypotheses. *Archives of General Psychiatry*, 64(3), 338-344.
- Davis, E. P., Glynn, L. M., Schetter, C. D., Hobel, C., Chicz-Demet, A., & Sandman, C. A. (2007). Prenatal exposure to maternal depression and cortisol influences infant temperament. *Journal of the American Academy of Child and Adolescent Psychiatry*, 46(6), 737-746.
- Del Cerro, M., Perez-Laso, C., Ortega, E., Martin, J., Gomez, F., & Perez-Izquierdo, M. (2010): Maternal care counteracts behavioral effects of prenatal environmental stress in female rats. *Behavioral Brain Research*, 208, 593-602.
- Gordon, I., Voos, A. C., Bennett, R. H., Bolling, D. Z., Pelphrey, K. A., & Kaiser, M. D. (2013). Brain mechanisms for processing affective touch. *Human Brain Mapping*, 34(4), 914-922.
- Gordon, I., Voos, A. C., Bennett, R. H., Bolling, D. Z., Pelphrey, K. A., & Kaiser, M. D. (2013). Brain mechanisms for processing affective touch. *Human Brain Mapping*, 34(4), 914-922.

- Hill, J., Pickles, A., Wright, N., Quinn, P., Murgatroyd, C., & Sharp, H. (2017). Maternal depression and child behaviors: sex-dependent mediation by glucocorticoid receptor gene methylation in a longitudinal study from pregnancy to age 5 years.
- Koukounari, A., Pickles, A., Hill, J., & Sharp, H. (2015). Psychometric Properties of the Parent-Infant Caregiving Touch Scale. *Frontiers in Psychology*, 6.
- Lemaire, V., Lamarque, S., Le Moal, M., Piazza, P.-V., & Abrous, D. N. (2006). Postnatal stimulation of the pups counteracts prenatal stress-induced deficits in hippocampal neurogenesis. *Biological Psychiatry*, 59(9), 786-792.
- Meaney, M. J. (2010). Epigenetics and the biological definition of gene $\times$ environment interactions. *Child Development*, 81(1), 41-79.
- Moffitt, T. E., Caspi, A., Krueger, R. F., Magdol, L., Margolin, G., Silva, P. A., & Sydney, R. (1997). Do partners agree about abuse in their relationship?: A psychometric evaluation of interpartner agreement. *Psychological Assessment*, 9(1), 47.
- Murgatroyd, C., Quinn, J., Sharp, H., Pickles, A., & Hill, J. (2015). Effects of prenatal and postnatal depression, and maternal stroking, at the glucocorticoid receptor gene. *Translational Psychiatry*, 5(5), e560.
- Noble, M., Wright, G., Dibben, C., Smith, G., McLennan, D., & Antila, C. (2004). The English Indices of Deprivation 2004 (revised). Report to the Office of the Deputy Prime Minister. London: Neighbourhood Renewal Unit.
- O'Connor, T. G., Heron, J., Golding, J., & Glover, V. (2003). Maternal antenatal anxiety and behavioral/emotional problems in children: a test of a programming hypothesis. *Journal of Child Psychology and Psychiatry*, 44(7), 1025-1036.
- O'Connor, T. G., Ben-Shlomo, Y., Heron, J., Golding, J., Adams, D., & Glover, V. (2005). Prenatal anxiety predicts individual differences in cortisol in pre-adolescent children. *Biological Psychiatry*, 58(3), 211-217.

- O'Donnell, K. J., Glover, V., Barker, E. D., & O'Connor, T. G. (2014). The persisting effect of maternal mood in pregnancy on childhood psychopathology. *Development and Psychopathology*, 26(2), 393-403.
- Pickles, A., Sharp, H., Hellier, J., & Hill, J. (2017). Prenatal anxiety, maternal stroking in infancy, and symptoms of emotional and behavioral disorders at 3.5 years. *European Child & Adolescent Psychiatry*, 26(3), 325-334.
- Quarini, C., Pearson, R. M., Stein, A., Ramchandani, P. G., Lewis, G., & Evans, J. (2016). Are female children more vulnerable to the long-term effects of maternal depression during pregnancy? *Journal of Affective Disorders*, 189, 329-335.
- Rabe-Hesketh, S., Skrondal, A., & Pickles, A. (2002). Reliable estimation of generalized linear mixed models using adaptive quadrature. *The Stata Journal*, 2(1), 1-21.
- Rothbart, M. K., Chew, K. H., & Gartstein, M. A. (2001). Assessment of temperament in early development. *Biobehavioral Assessment of the Infant*, 190-208.
- Sharp, H., Pickles, A., Meaney, M., Marshall, K., Tibu, F., & Hill, J. (2012). Frequency of infant stroking reported by mothers moderates the effect of prenatal depression on infant behavioral and physiological outcomes. *PLoS One*, 7(10), e45446.
- Sharp, H., Hill, J., Hellier, J., & Pickles, A. (2015). Maternal antenatal anxiety, postnatal stroking and emotional problems in children: outcomes predicted from pre-and postnatal programming hypotheses. *Psychological Medicine*, 45(02), 269-283.
- Spielberger, C. D. (1983). Manual for the State-Trait Anxiety Inventory STAI (form Y)(" self-evaluation questionnaire").
- Stringaris, A., & Goodman, R. (2009). Three dimensions of oppositionality in youth. *Journal of Child Psychology and Psychiatry*, 50(3), 216-223.
- Stringaris, A., Goodman, R., Ferdinando, S., Razdan, V., Muhrer, E., Leibenluft, E., & Brotman, M. A. (2012). The Affective Reactivity Index: a concise irritability scale for

clinical and research settings. *Journal of Child Psychology and Psychiatry*, 53(11), 1109-1117.

The Stata Journal 2.1 <http://www.stata-journal.com/sj2-1.html>

van den Bergh, B. R., Van Calster, B., Smits, T., Van Huffel, S., & Lagae, L. (2008). Antenatal maternal anxiety is related to HPA-axis dysregulation and self-reported depressive symptoms in adolescence: a prospective study on the fetal origins of depressed mood. *Neuropsychopharmacology*, 33(3), 536-545.

van Lieshout, R. J., & Boylan, K. (2010). Increased depressive symptoms in female but not male adolescents born at low birth weight in the offspring of a national cohort. *The Canadian Journal of Psychiatry*, 55(7), 422-430.

Vidal-Ribas, P., Brotman, M. A., Valdivieso, I., Leibenluft, E., & Stringaris, A. (2016). The status of irritability in psychiatry: a conceptual and quantitative review. *Journal of the American Academy of Child and Adolescent Psychiatry*, 55(7), 556-570.

Vidal-Ribas, P., Pickles, A., Tibu, F., Sharp, H., & Hill, J. (2017). Sex differences in the associations between vagal reactivity and oppositional defiant disorder symptoms. *Journal of Child Psychology and Psychiatry*.

Whelan, Y. M., Leibenluft, E., Stringaris, A., & Barker, E. D. (2015). Pathways from maternal depressive symptoms to adolescent depressive symptoms: the unique contribution of irritability symptoms. *Journal of Child Psychology and Psychiatry*, 56(10), 1092-1100.

Table 1 *Descriptive statistics for maternal and child variables*

	Boys			Girls		
	N	Mean	s.d.	N	Mean	s.d.
Prenatal anxiety	436	30.90	9.52	451	31.63	10.41
9 weeks postnatal anxiety	424	30.40	10.12	435	29.92	9.92
14 months postnatal anxiety	339	31.74	10.48	369	30.48	10.16
3.5 years postnatal anxiety	345	30.40	10.80	365	30.00	10.30
9 weeks stroking	436	3.88	0.70	451	3.86	0.70
CBCL Total – mother report	316	21.89	18.94	351	17.68	14.81
TRF Total – teacher report	296	16.63	19.06	331	9.31	13.18
Irritability – highest of mother/teacher	317	1.26	1.50	351	0.98	1.30
Headstrong- highest of mother/teacher	318	1.64	1.39	351	1.31	1.20
Stratum low	436	77%		451	75%	
Stratum mid		8%			7%	
Stratum high		16%			18%	
Maternal age <21 years	436	10%		451	12%	
Maternal age 21-30 years		56%			56%	
Maternal age >30 years		34%			32%	
Full time education only up to age 18	436	62%		451	67%	
Smoking – none	436	62%		451	64%	
Smoking before pregnancy		21%			19%	
Smoking during pregnancy		17%			18%	
No partner	436	17%		451	19%	
Most Deprived Quintile	436	37%		451	36%	

Table 2 *Summary of SEM for the interaction between prenatal-postnatal maternal anxiety and maternal stroking, predicting child irritability and headstrong symptoms at age 7 years*

	Irritability (N = 887)		Headstrong (N = 887)	
	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value
Prenatal maternal anxiety 20 weeks gestation	.038 (-.050, .126)	.397	.004 (-.091, .083)	.925
Postnatal maternal anxiety factor	-.149 -.607, .309	.523	.151 (-.157,.458)	.336
Maternal stroking 9 weeks postnatal	-.060 (-.142, .022)	.154	-.048 (-.130, .034)	.252
Prenatal anxiety by stroking	-.059 (-.140, .022)	.156	-.081 (-.159, -.003)	.043
Postnatal anxiety by stroking	-.067 (-.375, .241)	.668	.001 (-.322, .325)	.994
Prenatal anxiety by postnatal anxiety	-.129 (-.410, .154)	.372	-.225 (-.498, .047)	.105
Prenatal anxiety by postnatal anxiety by stroking	.533 (.221, .843)	.001	.128 -.169, .424	.399

All analyses controlled for area deprivation, maternal age, marital status, partner psychological abuse, and smoking, during pregnancy. Child irritability and headstrong symptoms were from combined maternal and teacher report.

Table 3 *Summary of SEM for the interaction between prenatal-postnatal maternal anxiety and maternal stroking, predicting child irritability and headstrong symptoms, including effects on, and of, general psychopathology estimated as total CBCL/TRF problem scores at age 7 years*

	Irritability (N = 669)		Headstrong (N = 669)		Total problem score (N = 669)	
	Coefficient 95% CI	p- value	Coefficient 95% CI	p- value	Coefficient 95% CI	p- value
Prenatal maternal anxiety 20 weeks	.049 -.022, .120	.116	.012 -.060, .083	.750	-.034 (-.120,.053)	.443
Postnatal maternal anxiety factor	-.171 -.429, .086	.179	-.259 -.536, -.018	.067	.659 (.343,.975)	<.001
Maternal stroking 9 weeks postnatal	-.041 -.108, .025	.288	-.031 -.097, .036	.371	-.017 (-.098,.063)	.669
Prenatal anxiety by stroking	-.047 -.112, .119	.333	-.076 -.141, -.011	.021	-.010 (-.088,.068)	.801
Postnatal anxiety by stroking	-.074 -.193, .340	.337	.215 -.068, .499	.137	-.311 (-.658,.034)	.077
Prenatal anxiety by postnatal anxiety	-.131 -.343, .087	.367	.239 -.448, .010	.041	.150 (-.134,.434)	.300
Prenatal anxiety by postnatal anxiety by stroking	.388 .145, .635	.002	-.002 -.238, .234	.986	.095 (-.206,.397)	.536
General psychopathology	.659 .343, .975	<.001	.701 .377, 1.026	<.001		

Figure 1. Summary of SEM for prediction of child irritability accounting for general psychopathology from prenatal and postnatal maternal anxiety and stroking

Main effects are shown in black, interactions in red and potential mediation of effects via general psychopathology 'p' in blue.

Figure 2. Associations between maternal stroking at 9 weeks and child irritability at 7 years, in matched and mismatched prenatal and postnatal maternal anxiety groups