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Mothers' Global Psychological Health and Sex-specific Expression in Newborns

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Abstract

Summary: The prenatal environment can influence gene expression involved in the development, possibly contributing to generational patterns of psychological health. Moreover, sex-specific developmental differences in-utero may result in gene expression differences associated with the prenatal environment. However, it is not clear if maternal overall psychological symptoms will associate with newborn's gene expression, or if such patterns are consistent between sexes. This study explored the relationships between maternal psychological health (PsyH) and newborn's gene expression patterns. We assessed PsyH with the Brief Symptom Inventory and newborn gene expression in umbilical cord blood. We conducted combined and sex-stratified analyses of genes expressed in umbilical cord blood.

Findings: PsyH associated with differential expression of 157 genes in males. The 157 differentially expressed genes are more likely to function in metabolic processes. There were no significant differences in gene expression in females.

Application: The sex-specific nature of these findings suggests males may be more vulnerable than females to mothers' psychological functioning during pregnancy. It is possible that the male-specific results are due in part to female newborns developing under different neuroendocrine conditions. Future research examining prenatal exposures should consider sex differences.

Introduction

Prenatal development is sensitive to maternal stress which can have lasting effects on neonate health[1,2]. Furthermore, males and females have shown differences in prenatal stress programming that could represent different health and developmental risks according to neonate sex[3]. Maternal psychological health is one maternal stress factor linked to prenatal development[4] in a sex-specific manner[5] that may represent sex-specific biological embedding. Maternal psychological health has been measured in different ways showing varying associations with neonate health. For example, mothers with greater affect intensity showed greater fetal motor activity during pregnancy compared to mothers with more stable affect[6]. Moreover, depression or anxiety during pregnancy associated with more difficult neonate temperaments[7]. The links between maternal psychological health and neonate health can best be explained by the process of experience influencing developmental processes, termed "biological embedding"[8].

Biological Embedding

Pregnancy can be stressful for the mother[9] and the additional

burden of psychological symptoms can affect the fetus' developing brain. Previous findings showed mother and newborn hypothalamus-pituitary-adrenal (HPA) axis functioning was linked to cortisol activity and suggested the HPA axis had been sensitized to stress and stimulation in neonates[10] through the process of fetal programming[11]. Chronic stress activation can influence a sensitized HPA axis which can affect the immune system and metabolism[12]. These physiological adaptations increase a child's vulnerability to environmental insults during neurodevelopment. Collectively the research suggests that women who suffer psychological health symptoms are at increased risk to have children with a greater vulnerability to stress.

Emerging evidence suggests that the mothers' psychological health during pregnancy, can impose fetal stress that influences gene expression and fetal development[13-15]. Moreover, there are developmental differences between male and female embryos resulting in varying sensitivities to the prenatal environment. For example, male fetuses undergo an epigenetic process during pregnancy to masculinize the brain[16]. The potential for sex-specific variation in sensitivity to the prenatal environment underscores the need to examine sex-specific effects within the context of maternal psychological health. Sex-specific differences in gene expression may help explain sex-specific risk and resilience within childhood psychopathology[17] as well as affective disorders found in adulthood, i.e. anxiety, bipolar disorder, depression, and post-traumatic stress disorder[18].

This study aimed to determine if: 1) maternal psychological health during pregnancy will associate with gene expression in newborns, and 2) the association between maternal psychological health and newborn gene expression is sex-specific.

Results

Subjects are primarily African American mothers (African American 62% vs. Caucasian 38%) of similar age (25.04 ± 5.15 vs. 28.56 ± 4.61) and the newborns are comparably distributed between sexes (male [n = 61, 55%], female [n = 50, 45%]). The majority of the mothers reported some degree of PsyH symptoms (M = 50.33, SD = 7.79) that did not differ according to newborn sex (p = .18) (see Figures 1 and 2).

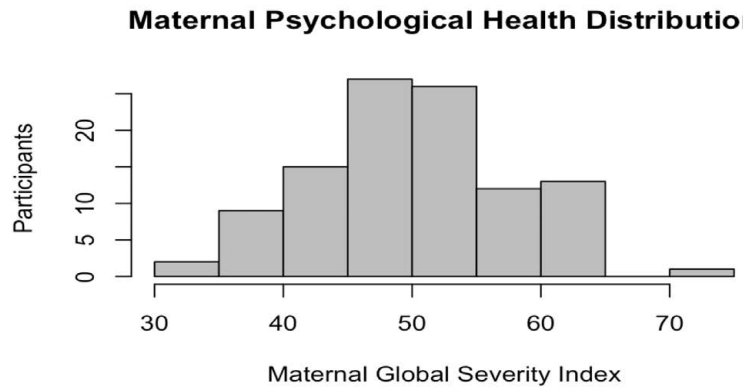

Figure 1: Histogram of Maternal Psychological Health Distribution in Full Neonate Cohort. PsyH is relatively normally distributed with a score range of 33-72 (n = 111, M = 50.33, SD = 7.8, $skew$ = .06, $kurtosis$ = -.32, SE = .76).

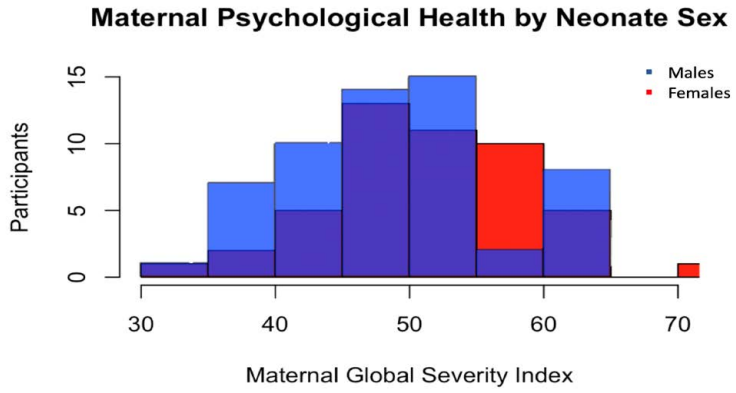

Figure 2: Maternal Psychological Health Distribution by Neonate Sex. Male and female neonates show similar distributions of maternal psychological health symptoms.

Full Cohort Associations

PsyH did not associate with newborn gene expression in the full newborn cohort while controlling for sex, race and cell composition. However, gene expression did associate with newborn sex for 17 genes, although all were located on the sex chromosomes. Plots of the effect sizes and t-statistics for the gene expression probes according to newborn sex suggests male and female newborns responded differently to PsyH (see Figure 3). Therefore, we conducted a sex-stratified analysis to investigate possible gene expression associations with PsyH unique to male or female newborns.

Sex-stratified Cohort Associations

Males exhibited significant gene expression of 157 genes related to increases in PsyH scores during pregnancy (Supplemental Table 1). The 157 genes showed positive (38%) and negative (62%) associations, as modeled in a volcano plot (Figure 4), suggesting a complex interaction with the prenatal environment. These genes were enriched for a variety of metabolic functions (Table 1). For example, expression of the eukaryotic translation initiation factor 4E binding protein 2 (*EIF4EBP2*), a gene represented among multiple enriched biological processes is lower in males whose mothers have higher levels of PsyH symptoms

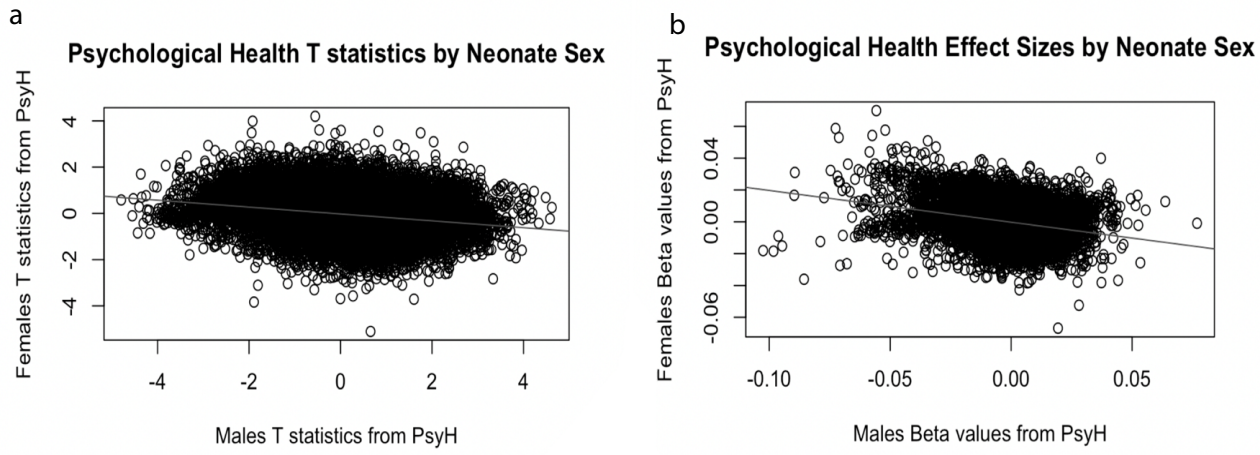

Figure 3: Plots by Newborn Sex of Association Indicators for Psychological Health. a: t-statistics show an inverse association between males and females. b: The beta values show an inverse association for gene expression and psychological health according to newborn sex.

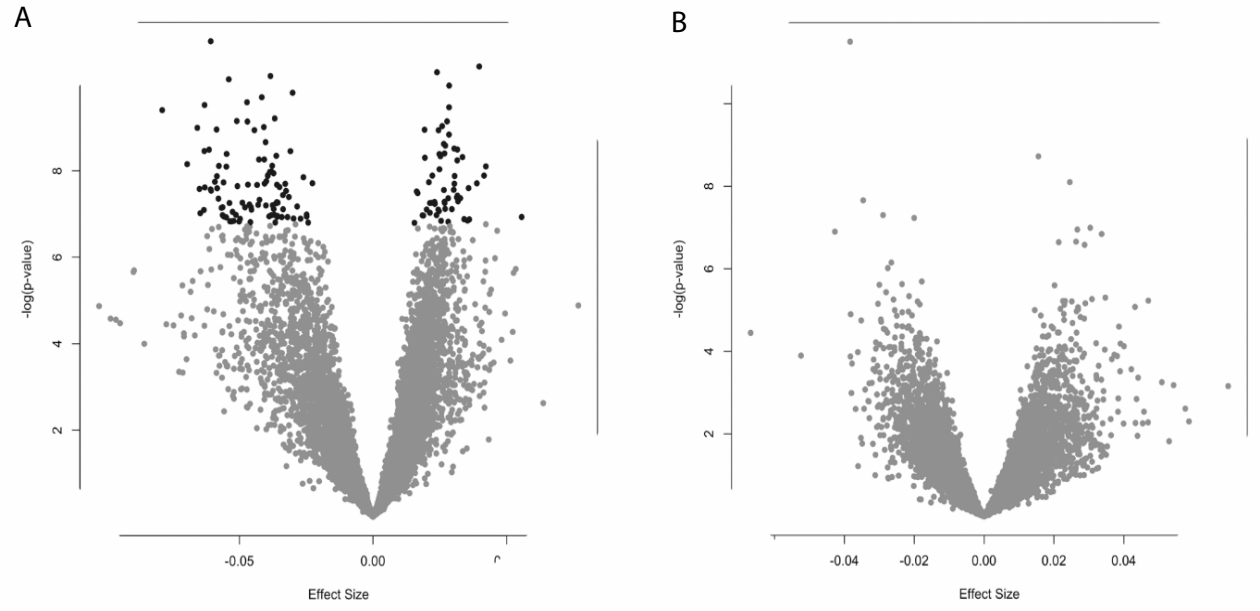

Figure 4: Volcano plot comparison of PsyH and gene expression association values by newborn sex. A: Males show more negative gene expression associations with maternal psychological health. B: Females show no gene expression associations with maternal psychological health.

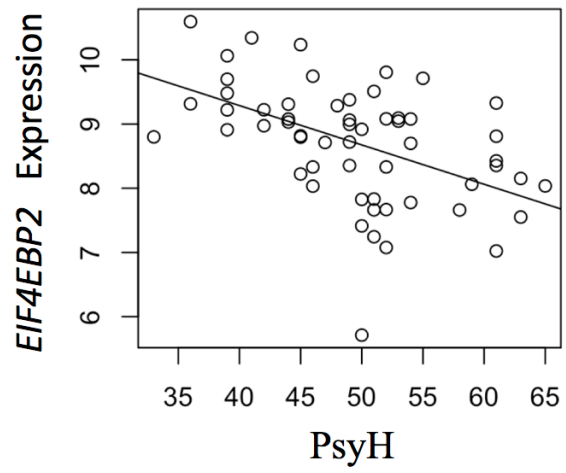

Figure 5: Maternal PsyH and *EIF4EBP2* Expression in Male Newborns. *EIF4EBP2* gene (ILMN_1728083) is shared among the metabolic pathways, is involved in inhibiting translation, and shows greater expression in males neonates with greater PsyH symptoms in moms. Analyses controlled for child race, cell composition, and multiple comparisons.

Table 1: Enrichment of Biological Processes Among Genes whose Expression associates with maternal PsyH in males.

Path Identifier	Description	# Genes	Bayes Factor	p-value
GO:0044237	cellular metabolism	46	7	.003
GO:0008152	metabolism	48	7	.003
GO:0043170	macromolecule metabolism	22	6	.005
GO:0044238	primary metabolism	44	6	.007

(Figure 5). Female newborns showed no gene expression associations with PsyH after controlling for covariates and adjusting for multiple comparisons (FDR > .05).

Discussion

Our findings suggest that maternal psychological health can influence the prenatal environment with gene expression associations unique to male newborns. These results suggest males may be more sensitive to maternal psychological health during pregnancy compared to females. Male newborns showed differential expression of 157 genes associated with greater detrimental maternal psychological health, and these genes were enriched for fundamental processes of metabolism. Moreover, a PubMed search of the 157 genes identified *EIF4EBP2* as a gene of particular interest. *EIF4EBP2* is involved in inhibiting translation initiation, which can affect the amount of protein produced.

Interestingly, EIF4EBP2 has been implicated in the mechanisms of Autism Spectrum Disorders in rodent models with increased ASD behaviors in mice with the gene knocked out[19]. Moreover, newborn expression of *EIF4EBP2* has been shown to associate with maternal inflammatory responses during pregnancy[20] that have been linked to maternal psychological health[21]. Although investigations are ongoing, EIF4EBP2 clearly plays an important role in health and the transmission of health from mother to child. The unique association for male newborns in relation to maternal psychological health, therefore, could be an indication of a sex-specific neonatal developmental response to the prenatal environment. At a minimum, our findings support previous research proposing mothers' psychological health is associated with gene expression in male newborns that could predispose risk for or resilience to metabolic disorders[22,23], enduring cognitive deficits[14,15], and increased stress sensitivity[5].

Maternal psychological health functioning during pregnancy should be investigated further. It is possible that some psychological health symptoms exert greater influence than others, or associate with male and female newborns differently. Future research would benefit from the inclusion of different psychological symptoms such as depression, anxiety, somatization, or combinations thereof to provide an examination of differences among symptom types. Furthermore, psychological health can influence other things such as nutrition, income, and social support which could each affect the prenatal environment.

Continuing exploration into gene expression patterns associated with prenatal variables has the potential to inform professionals seeking to foster resilience in vulnerable populations through innovative approaches to reduce risk. For example, prenatal screenings could include assessment for variables that increase the risk for adverse behavioural outcomes in offspring. Therefore, identified environmental interventions for the pregnant mother such as diet and stress reduction could be applied to foster resilience in the fetus, and later the newborn. There are many avenues to promote good psychological health through stress reduction techniques like mindfulness[24], breathing exercises[25], physical exercise[26], and social connectedness[27] to name a few. Moreover, behaviors like healthy sleep patterns[28] and playing a musical instrument[29] have been shown to promote positive emotions and emotion regulation that promote good maternal psychological health.

These study findings, in conjunction with previous findings[5,14,15], suggest prenatal exposure to maternal psychological illness is one link for intergenerational patterns of risk, and risks may be sex-specific. Future research may deepen our understanding of mechanisms involved in these intergenerational patterns, and thereby provide new opportunities to intervene for improved quality of life. For example, this avenue of research could bolster arguments for the ongoing need for universal prenatal care, proper affordable nutrition, and other services to support mothers and families.

There are some limitations to this study. The sample is from one urban population in west Tennessee and is not generalizable to other populations. However, our replication of an association between maternal psychological health and male newborn gene expression provides additional context with previous findings[5,14,15]. The sample size is modest for transcriptome-wide investigations, but the transcriptome-wide analysis is an excellent tool to discover unknown or unsuspected relationships. However, analysis of the whole transcriptome significantly increases the number of conducted tests. To account for those tests, and the decreased probability of committing type I errors, we controlled for multiple comparisons with the False Discovery Rate and calculated bootstrap 95% confidence intervals to show the accuracy of estimated relationships. Lastly, we investigated these relationships in umbilical cord blood, and there may be relationships in other tissues (i.e., placenta).

The findings from our study, in conjunction with previous research[30,31], suggest that social problems such as stress and psychological illness have potential to exert influence on human development across generations. Therefore, the design of interventions will benefit from biopsychosocial research, like gene expression studies, that will help illuminate pathways to risk and resilience. Knowledge like this could one day be used in screening measures to aid intervention and prevention strategies and in the design and targeting of services to those who are most in need.

Methods

Sample and Procedures

The data for this study is from the Conditions Affecting Neurocognitive Development and Learning in Early Childhood investigation (CANDLE), and the University of Tennessee Health Science Center Institutional Review Board approved all measures and procedures. This study was carried out in accordance with the Belmont Report ethical principles and guidelines for human subjects research. The sample (111 mother/infant pairs) consists of healthy mothers aged 16-40 years solicited in prenatal settings in Shelby County, Tennessee. Announcements and brochures containing information about the study were provided to all local gynecology clinics. Interested women contacted study personnel by telephone and were then screened for eligibility. Women meeting eligibility criteria were asked to visit one of two research clinics utilized for the study. Forty percent of interested women met eligibility criteria and were invited to participate. All participants signed informed consent documents, and participants under the age of eighteen years provided a parent signed informed consent. The participants provided umbilical cord blood samples immediately after birth for biological measures including gene expression. Umbilical cord blood has been used to measure newborn gene expression in multiple studies[32-35].

Measures

Mothers' psychological health (PsyH) status variable was created using the global severity index (GSI) summary score from the Brief Symptom Inventory (BSI) (Derogatis & Melisaratos, 1983). The Brief Symptom Inventory is a shortened version of the SCL-90 psychological health assessment and has been found to be sensitive to psychopathology and psychological distress[36]. The global severity index score has been investigated and found to be a more accurate assessment of overall psychological health functioning than the positive symptom total score in the BSI measure[37].

Gene Expression

Gene expression is assessed by measuring the RNA transcript levels[38]. The Illumina Human WG-6 expression array was used to measure RNA transcription. Samples with less than 10% of the gene probes detected were eliminated, as well as probes with less than 10% of the samples detected within each dataset. No sample was lost based on these QC criteria. We performed quantile normalization, scaled the data, and performed a log2 transformation. Prior to analysis, updated annotation files for the Illumina Human WG-6 array were consulted for accurate gene expression measurement information[39]. A total of 10,821 expressed genes passed QC in these umbilical cord blood samples.

Statistical Analyses

Descriptive statistics were calculated to determine sample characteristics. We examined the association between PsyH and newborn transcriptome-wide gene expression as measured with the Illumina HumanWG-6 BeadChip. We performed multiple regression to conduct the newborn gene expression analyses and controlled for child sex, child race, and cell composition. Cell composition was estimated for each sample as previously described[40]. We statistically analyzed the cohort first and then conducted sex-stratified analyses controlling for child race and cell composition. Gene ontology analysis was performed on genes identified as significant using GATHER[41]. Bootstrap confidence intervals were generated to address potential non-normality of the data. As is standard in genetics research, we implemented the False Discovery Rate control for multiple comparisons in all gene expression analyses[42].

Acknowledgements

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References

1. Painter R, Osmond C, Gluckman P, et al. Transgenerational effects of prenatal exposure to the Dutch famine on neonatal adiposity and health in later life. BJOG: An International Journal of Obstetrics & Gynaecology. 2008; 115: 1243-1249.
2. Almond D, Mazumder B. Health capital and the prenatal environment: the effect of Ramadan observance during pregnancy. American Economic Journal: Applied Economics. 2011; 3: 56-85.
3. Glover V, Hill J. Sex differences in the programming effects of prenatal stress on psychopathology and stress responses: an evolutionary perspective. Physiology & Behavior. 2012; 106: 736-740.
4. Weinstock M. The potential influence of maternal stress hormones on development and mental health of the offspring. Brain behavior and immunity. 2005; 19: 296-308.
5. Mueller BR, Bale TL. Sex-Specific Programming of Offspring Emotionality Following Stress Early in Pregnancy. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2008; 28: 9055-9065. doi:10.1523/JNEUROSCI.1424-08.2008.
6. DiPietro JA, Hilton SC, Hawkins M, et al. Maternal stress and affect influence fetal neurobehavioral development. Developmental psychology. 2002; 38: 659.
7. Davis EP, Glynn LM, Schetter CD, et al. Prenatal Exposure to Maternal Depression and Cortisol Influences Infant Temperament. Journal of the American Academy of Child & Adolescent Psychiatry. 2007; 46: 737-746, doi:https://doi.org/10.1097/chi.0b013e318047b775.
8. Hertzman C. Putting the concept of biological embedding in historical perspective. Proceedings of the National Academy of Sciences. 2012; 109: 17160-17167.
9. Geller PA. Pregnancy as a Stressful Life Event. CNS Spectrums. 2004; 9: 188-197, doi:10.1017/S1092852900008981.
10. Brand SR, Brennan PA, Newport DJ, et al. The impact of maternal childhood abuse on maternal and infant HPA axis function in the postpartum period. Psychoneuroendocrinology. 2010; 35: 686-693.
11. Kapoor A, Dunn E, Kostaki A, et al. Fetal programming of hypothalamo-pituitary-adrenal function: prenatal stress and glucocorticoids. The Journal of physiology. 2006; 572: 31-44.
12. Perry. Examining child maltreatment through a neurodevelopmental lens: Clinical applications of the neurosequential model of therapeutics. Journal of Loss and Trauma. 2009; 14: 240-255.
13. Babenko O, Kovalchuk I, Metz GAS. Stress-induced perinatal and transgenerational epigenetic programming of brain development and mental health. Neuroscience and Biobehavioral Reviews. 2015; 48: 70-91. doi:http://dx.doi.org/10.1016/j.neubiorev.2014.11.013.
14. Kapoor A, Kostaki A, Janus C, et al. The effects of prenatal stress on learning in adult offspring is dependent on the timing of the stressor. Behavioural Brain Research. 2009; 197: 144-149, doi:http://dx.doi.org/10.1016/j.bbr.2008.08.018.
15. Lemaire V, Koehl M, Le Moal M, et al. Prenatal Stress Produces Learning Deficits Associated with an Inhibition of Neurogenesis in the Hippocampus. Proceedings of the National Academy of Sciences of the United States of America. 2000; 97: 11032-11037.
16. Bale. Epigenetic and transgenerational reprogramming of brain development. Nat Rev Neurosci. 2015; 16: 332-344, doi:10.1038/nrn3818.
17. Gray SA, Theall K, Lipschutz R, et al. Sex differences in the contribution of respiratory sinus arrhythmia and trauma to children's psychopathology. Journal of psychopathology and behavioral assessment. 2017; 39: 67-78.
18. Altemus M, Sarvaiya N, Epperson CN. Sex differences in anxiety and depression clinical perspectives. Frontiers in neuroendocrinology. 2014; 35: 320-330, doi:10.1016/j.yfrne.2014.05.004.
19. Gkogkas CG, Khoutorsky A, Ran I, et al. Autism-related deficits via dysregulated eIF4E-dependent translational control. Nature. 2013; 493: 371.
20. Zhou J, Zhang X, Zhang H, et al. Use of data mining to determine changes in the gene expression profiles of rat embryos following prenatal exposure to inflammatory stimulants. Molecular medicine reports. 2013; 8: 95-102.
21. Christian LM. Stress and Immune Function during Pregnancy: An Emerging Focus in Mind-Body Medicine. Curr Dir Psychol Sci. 2015; 24: 3-9, doi:10.1177/0963721414550704.
22. Harris A, Seckl J. Glucocorticoids, prenatal stress and the programming of disease. Hormones and Behavior. 2011; 59: 279-289, doi:https://doi.org/10.1016/j.yhbeh.2010.06.007.
23. Tamashiro KLK, Moran TH. Perinatal environment and its influences on metabolic programming of offspring. Physiology & Behavior. 2010; 100: 560-566, doi:https://doi.org/10.1016/j.physbeh.2010.04.008.
24. Khoury B, Sharma M, Rush SE, et al. Mindfulness-based stress reduction for healthy individuals: A meta-analysis. Journal of psychosomatic research. 2015; 78: 519-528.
25. Varvogli L, Darviri C. Stress Management Techniques: evidence-based procedures that reduce stress and promote health. Health science journal. 2011; 5-74.
26. Yau SY, Lau BWM, So KF. Adult hippocampal neurogenesis: a possible way how physical exercise counteracts stress. Cell Transplantation. 2011; 20: 99-111.
27. Haslam C, Cruwys T, Haslam SA, et al. Social connectedness and health. Encyclopaedia of geropsychology. 2015; 46-41.
28. Shen L, van Schie J, Ditchburn G, et al. Positive and negative emotions: Differential associations with sleep duration and quality in adolescents. Journal of youth and adolescence. 2018; 47: 2584-2595.
29. Moore KS. A systematic review on the neural effects of music on emotion regulation: implications for music therapy practice. Journal of music therapy. 2013; 50: 198-242.
30. Meaney MJ. Maternal care, gene expression, and the transmission of individual differences in stress reactivity across generations. Annual review of neuroscience. 2001; 24: 1161-1192.
31. Yehuda R, Bierer LM. Transgenerational transmission of cortisol and PTSD risk. Progress in brain research. 2007; 167: 121-135.
32. Adkins RM, Krushkal J, Tylavsky FA, et al. Racial differences in gene-specific DNA methylation levels are present at birth. Birth Defects Research Part A: Clinical and Molecular Teratology. 2011; 91: 728-736.
33. Adkins RM, Thomas F, Tylavsky FA, et al. Parental ages and levels of DNA methylation in the newborn are correlated. BMC medical genetics. 2011; 12: 47.
34. Adkins RM, Tylavsky FA, Krushkal J. Newborn umbilical cord blood DNA methylation and gene expression levels exhibit limited association with birth weight. Chemistry & biodiversity. 2012; 9: 888-899.
35. Krushkal J, et al. Epigenetic analysis of neurocognitive development at 1 year of age in a community-based pregnancy cohort. Behavior genetics. 2014; 44: 113-125.
36. Sitarenios G, Kovacs M, Maruish M. The use of psychological testing for treatment planning and outcomes assessment. Use of the Children's Depression Inventory. 1999; 267-298.
37. Derogatis LR, Melisaratos N. The brief symptom inventory: an introductory report. Psychological medicine. 1983; 13: 595-605.
38. Marioni JC, Mason CE, Mane SM, et al. RNA-seq: an assessment of technical reproducibility and comparison with gene expression arrays. Genome research. 2008; 18: 1509-1517.

39. Arloth J, Bader DM, Röh S, et al. Re-Annotator: Annotation Pipeline for Microarray Probe Sequences. PloS one. 2015; 10: e0139516, doi:10.1371/journal.pone.0139516.

40. Mozhui K, Smith AK, Tylavsky FA. Ancestry dependent DNA methylation and influence of maternal nutrition. PloS one. 2015; 10: e0118466.

41. Chang JT, Nevins JR. GATHER: a systems approach to interpreting genomic signatures. Bioinformatics (Oxford, England). 2006; 22: 2926-2933, doi:10.1093/bioinformatics/btl483.

42. Storey JD, Taylor JE, Siegmund D. Strong control, conservative point estimation and simultaneous conservative consistency of false discovery rates: a unified approach. Journal of the Royal Statistical Society: Series B (Statistical Methodology). 2004; 66: 187-205.

Supplemental Table

Genes differentially expressed in male newborns according to maternal PsyH

Probe ID	Gene	Beta Coefficient	Bootstrap 95% CI	FDR adjusted p-value	Probe ID	Gene	Beta Coefficient	Bootstrap 95% CI	FDR adjusted p-value
ILMN_2185264	ZNF461	-0.078886042	-.119, -.038	0.039400571	ILMN_2126802	RPS27L	-0.054882677	-.084, -.029	0.044812759
ILMN_1762573	LOC401630	-0.069570218	-.108, -.035	0.044812759	ILMN_2058841	LILRA6	-0.054787834	-.083, -.025	0.043364783
ILMN_2096442	LOC260339	-0.065750621	-.097, -.032	0.039400571	ILMN_2380101	PHACTR4	-0.053983378	-.070, -.030	0.039400571
ILMN_1746917	LOC729843	-0.064957403	-.084, -.038	0.045569436	ILMN_2190850	PPID	-0.053745272	-.086, -.025	0.047760063
ILMN_2175737	ZNF826	-0.064650594	-.099, -.023	0.048165878	ILMN_2179579	SNHG3	-0.053519627	-.085, -.024	0.049176039
ILMN_2198823	H6PD	-0.063303215	-.098, -.031	0.047760063	ILMN_2106002	ACBD7	-0.052888042	-.085, -.027	0.049176039
ILMN_2404320	SNTN	-0.06312612	-.095, -.033	0.043364783	ILMN_2395496	KLK7	-0.052570497	-.087, -.020	0.048165878
ILMN_1698766	PYCARD	-0.063042137	-.082, -.041	0.039400571	ILMN_2115011	FGD2	-0.052162454	-.082, -.024	0.049176039
ILMN_2141523	MRPL44	-0.06294615	-.097, -.029	0.045569436	ILMN_2084489	ZNF595	-0.051316734	-.082, -.019	0.048165878
ILMN_2402499	SC4MOL	-0.06135017	-.089, -.035	0.043364783	ILMN_2215965	CYP2B6	-0.050994618	-.074, -.024	0.039400571
ILMN_2203876	CCDC68	-0.060809072	-.094, -.027	0.045569436	ILMN_1712357	HNRPK	-0.050745076	-.074, -.025	0.045569436
ILMN_1876838		-0.060756232	-.088, -.039	0.039400571	ILMN_1757914	C19orf56	-0.050123353	-.072, -.027	0.049176039
ILMN_1715635	ATP6V0E1	-0.060589336	-.095, -.033	0.045569436	ILMN_1741491	ZNHIT1	-0.049742067	-.083, -.026	0.048871645
ILMN_2357377	TERF1	-0.059190782	-.091, -.027	0.045569436	ILMN_2178186	PIGW	-0.04887585	-.076, -.022	0.047760063
ILMN_2208491	RPLP0P2	-0.058546721	-.089, -.036	0.039400571	ILMN_2127416	GSR	-0.047914114	-.073, -.028	0.047760063
ILMN_2066249	RPP30	-0.058426512	-.095, -.031	0.045569436	ILMN_1671494	USP5	-0.047160548	-.068, -.032	0.039400571
ILMN_2217955	TTC21B	-0.058323114	-.091, -.029	0.045569436	ILMN_1689710	C16orf50	-0.047007495	-.069, -.026	0.039400571
ILMN_2281089	STEAP3	-0.057859572	-.092, -.025	0.047760063	ILMN_2102580	UTP20	-0.046813344	-.071, -.021	0.045569436
ILMN_1679809	GSTP1	-0.057681223	-.088, -.031	0.044812759	ILMN_2409720	SLA2	-0.04625212	-.070, -.018	0.047760063
ILMN_1651358	HBE1	-0.056699663	-.081, -.020	0.047760063	ILMN_2245686	GYG2	-0.045899964	-.073, -.018	0.049176039
ILMN_2346562	ZNF273	-0.056319333	-.090, -.029	0.048165878	ILMN_1765621	HDGF	-0.045702693	-.068, -.020	0.047760063
ILMN_2382657	ARHGAP9	-0.056298906	-.086, -.027	0.047760063	ILMN_1917044		-0.045493069	-.072, -.030	0.047760063
ILMN_2049228	NUDT4P1	-0.055937291	-.086, -.028	0.045569436	ILMN_1756942	SP3	-0.044384942	-.056, -.025	0.039400571
ILMN_2180997	GTF2IRD2B	-0.055805828	-.088, -.031	0.048165878	ILMN_2151168	SLC30A6	-0.043380056	-.065, -.019	0.045569436
ILMN_1728083	EIF4EBP2	-0.054931752	-.080, -.032	0.048165878	ILMN_2378670	SNX15	-0.043006845	-.067, -.016	0.047760063
ILMN_2070477	TAF8	-0.042691067	-.064, -.020	0.043364783	ILMN_2137464	DVL3	-0.035973219	-.055, -.017	0.047760063
ILMN_1715698	MGC71993	-0.042485825	-.064, -.020	0.047760063	ILMN_2145143	FKBP9	-0.035961146	-.052, -.012	0.045569436
ILMN_2292696	COX15	-0.041623601	-.062, -.028	0.039400571	ILMN_2331658	C3orf17	-0.03585831	-.054, -.017	0.048165878
ILMN_1742400	CEP350	-0.040846365	-.054, -.022	0.039400571	ILMN_1794522	EIF5A	-0.035854562	-.061, -.019	0.048165878
ILMN_2280441	PACRG	-0.040702491	-.059, -.017	0.043364783	ILMN_2141030	LOC641522	-0.035638955	-.054, -.014	0.047760063
ILMN_2042941	TMEM159	-0.040579203	-.059, -.019	0.045569436	ILMN_1797964	ARL6IP6	-0.024273555	-.030, -.004	0.049176039
ILMN_1758100	GALR3	-0.040217106	-.060, -.019	0.043364783	ILMN_1773850	FXC1	-0.022685488	-.035, -.011	0.045569436
ILMN_1739792	RHOG	-0.040075792	-.061, -.018	0.047760063	ILMN_1682736	LOC643452	0.01550105	.004, .024	0.049177556
ILMN_2410362	ACBD5	-0.039916622	-.059, -.018	0.045569436	ILMN_1675852	LOC650518	0.016336257	.008, .026	0.04559356
ILMN_2055271	A1BG	-0.039415396	-.056, -.017	0.045569436	ILMN_1721713	EXOSC9	0.016725851	.006, .025	0.04681483
ILMN_2358652	NXF1	-0.039356826	-.062, -.019	0.045569436	ILMN_1659523	USP39	0.018544909	.003, .024	0.048165878
ILMN_2374383	TSPAN17	-0.038850669	-.059, -.021	0.048165878	ILMN_1776347	TCP1	0.018823076	.009, .026	0.048165878
ILMN_2162972	LYZ	-0.03863507	-.055, -.016	0.045569436	ILMN_1767992	SLC12A6	0.019306512	.009, .029	0.039400571
ILMN_1651506	NCOA6IP	-0.038395972	-.049, -.019	0.039400571	ILMN_1704206	NPSR1	0.019418619	.0003, .024	0.043364783
ILMN_1682938	ARF3	-0.038045144	-.060, -.014	0.048165878	ILMN_2192683	DHX37	0.020070541	.007, .026	0.047760063
ILMN_2277252	PPFIBP1	-0.038031935	-.055, -.017	0.045569436	ILMN_1662896	BRWD2	0.0209141	.009, .030	0.045569436
ILMN_2178201	ZNF43	-0.037734631	-.055, -.018	0.044812759	ILMN_1776147	C21orf59	0.021299857	.008, .031	0.048165878
ILMN_2255142	TRIM34	-0.037587268	-.057, -.013	0.047760063	ILMN_1727761	GMEB1	0.021302431	.006, .026	0.047760063
ILMN_2115974	GSDM1	-0.037211655	-.055, -.014	0.045569436	ILMN_1693421	RPN2	0.022035022	.010, .032	0.047760063
ILMN_1660869	LOC643438	-0.037161222	-.056, -.020	0.047760063	ILMN_1725169	INTS12	0.022214042	.005, .034	0.045569436
ILMN_1750805	ARHGAP30	-0.036936857	-.053, -.023	0.048165878	ILMN_1737413	MSH2	0.023029546	.005, .030	0.047760063
ILMN_2261600	FCGR1B	-0.036794728	-.046, -.017	0.039400571	ILMN_1916094		0.023133907	.009, .035	0.047760063
ILMN_1684434	SLC17A5	-0.036576672	-.057, -.014	0.049176039	ILMN_1677376	CHD7	0.023791824	.012, .037	0.048165878
ILMN_2190851	PPID	-0.036289407	-.052, -.014	0.047760063	ILMN_1774974	CLUAP1	0.023952943	.011, .030	0.039400571
ILMN_2196232	C1orf210	-0.036197628	-.052, -.016	0.043364783	ILMN_1748018	GORASP2	0.02441163	.010, .032	0.047760063
ILMN_2359096	SS18	-0.034992783	-.053, -.015	0.045569436	ILMN_1801833	ARHGAP24	0.024525524	.015, .038	0.039400571
ILMN_2252136	YWHAE	-0.034150242	-.060, -.021	0.048165878	ILMN_1771801	SIRPG	0.024716906	.012, .036	0.048165878
ILMN_2406532	F11R	-0.033700911	-.051, -.011	0.047760063	ILMN_1684724	CR2	0.024839519	.012, .037	0.043364783
ILMN_2263236	HFE	-0.033652648	-.053, -.014	0.047760063	ILMN_2136133	PABPC1	0.024864516	.010, .033	0.045569436
ILMN_2299795	CPM	-0.032837325	-.045, -.010	0.045569436	ILMN_1720270	CDR2	0.025226775	.006, .032	0.043364783
ILMN_1728957	ANKRD5	-0.032553034	-.049, -.012	0.045569436	ILMN_1789653	PBLD	0.025480103	.010, .038	0.049176039
ILMN_1775919	C6orf79	-0.031994525	-.049, -.013	0.048165878	ILMN_2048822	NUDCD2	0.025886067	.013, .033	0.039400571

ILMN_2323302	SON	-0.031503972	-.051, -.018	0.047760063		ILMN_1655625	GPATCH1	0.026500147	.007, .041	0.043364783
ILMN_1810488	NFYC	-0.030915679	-.044, -.012	0.043364783		ILMN_1725175	FOSL2	0.02654905	.010, .039	0.045569436
ILMN_1712400	SERPINB6	-0.030091528	-.042, -.017	0.039400571		ILMN_1749586	LOC642914	0.026746809	.016, .046	0.047760063
ILMN_1770673	AKNA	-0.029749607	-.043, -.009	0.048871645		ILMN_1717852	USH1G	0.026754287	.016, .039	0.043364783
ILMN_2144116	CPSF2	-0.02838741	-.040, -.012	0.047760063		ILMN_2156953	ZFAND6	0.026820464	.015, .036	0.047760063
ILMN_1730879	CBY1	-0.027131446	-.039, -.014	0.048871645		ILMN_2186482	TMED7	0.026990153	.015, .043	0.047760063
ILMN_1744113	TNFAIP8L2	-0.026052743	-.034, -.008	0.045569436		ILMN_1672446	RPL11	0.027072111	.008, .040	0.043364783
ILMN_2122022	ZNF639	-0.024844573	-.038, -.010	0.048165878		ILMN_1704956	SMTNL1	0.027710644	.007, .039	0.039400571
ILMN_1807649	SPOPL	-0.024839798	-.029, -.007	0.048165878		ILMN_1818935		0.028159219	.016, .044	0.047760063
ILMN_1692535	DPP4	0.028160224	.012, .036	0.049176039		ILMN_2130525	TSPAN13	0.031815095	.015, .043	0.047760063
ILMN_2114876	RPL11	0.028446346	.009, .043	0.04180435		ILMN_2381064	TPD52	0.032692639	.017, .050	0.047760063
ILMN_1764323	LOC124512	0.028469498	.016, .040	0.039400571		ILMN_1652085	MPHOSPH10	0.033498448	.017, .048	0.043364783
ILMN_2410771	KEAP1	0.028499536	.008, .033	0.039400571		ILMN_1657873	XPO4	0.034105854	.017, .054	0.048871645
ILMN_1853160		0.029498432	.017, .044	0.047760063		ILMN_2200636	KIAA1267	0.035372831	.017, .048	0.049176039
ILMN_1653129	CSTF2	0.030208328	.013, .039	0.045569436		ILMN_1909223		0.035757529	.017, .050	0.045569436
ILMN_1730791	LOC646783	0.030379729	.015, .043	0.043364783		ILMN_2103774	PIP5KL1	0.036060422	.014, .047	0.048871645
ILMN_2151048	STAG1	0.030436997	.019, .041	0.045569436		ILMN_1837286		0.038877769	.019, .055	0.045569436
ILMN_1880113		0.030540174	.013, .045	0.045569436		ILMN_1819251		0.039768665	.019, .053	0.039400571
ILMN_1879078		0.031327435	.013, .047	0.047760063		ILMN_2379788	HIF1A	0.041570256	.028, .062	0.045569436
ILMN_1888252		0.031513924	.015, .048	0.043364783		ILMN_1798874	TMEM85	0.042248923	.018, .057	0.044812759
ILMN_1662845	NBPF11	0.031580898	.018, .049	0.043364783		ILMN_2379762	NPM1	0.055644091	.027, .087	0.048165878
ILMN_1748141	AMOTL1	0.031599523	.015, .048	0.047760063						