Washington University Journal of Law & Policy

Volume 57 *BRINGING SCIENCE TO LAW AND POLICY*

2018

A Role of Early Life Stress on Subsequent Brain and Behavioral Development

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ABSTRACT

The prevalence of pediatric neuropsychiatric disorders has risen dramatically during the past two decades. A study surveying the years 1997-2008 verified that one in six children have a developmental disability—a number on the rise. Along similar lines, studies show higher incidents of criminal activity, substance use disorders, and the emergence of psychopathologies in early adolescence and young adulthood, which are particularly sensitive periods of brain and behavioral maturation. While developmental trajectories that may lead to adverse outcomes in youth are the result of a mix of genetics and environmental exposure, it is becoming clearer that they do not start at the time of the diagnosis or problem behaviors; rather, these developmental trajectories start at the earliest periods of life. The ability of children to achieve their full physical, academic, and social potential is tightly related to early life events, some of which may occur even before birth. The science is now amassed with investigators and research targeting the role of Early Life Stress and its interaction with biological systems in impacting the development of the brain and complex behaviors across all stages development.

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I. A ROLE OF EARLY LIFE STRESS ON SUBSEQUENT BRAIN AND BEHAVIORAL DEVELOPMENT

Developmental neuropsychiatric disorders are a major public health concern that entails massive costs, leads to extensive hardship for children and families, contributes to serious negative long-term outcomes, and places substantial demands on the nation's educational and health care systems.[1] These consequences highlight the need for innovative approaches to understanding etiology, and ultimately improve treatment and preventative strategies for a range of disorders. Indeed, one in six children now have a developmental disability—a seventeen percent increase in children over the past decade, driven largely by increases in Autism Spectrum Disorder (ASD) and Attention Deficit Hyperactivity Disorder (ADHD).[2]

We note that typical development can put pressure on the health of our society. For example, even before the earliest conceptions of a juvenile justice system, adolescents and young adults have presented unique challenges to policy-makers.[3] Studies reveal higher incidents of criminal activity, substance use disorders, and the emergence of psychopathologies during this sensitive time period amongst a range of potentially comorbid factors.[4] In subsets of adolescents, the propensity for increased risky behaviors, higher degrees of sensation seeking and impulsivity, greater

1. Joshua Breslau, et al., *The Impact of Early Behavior Disturbances on Academic Achievement in High School*, 123 PEDIATRICS 1472, https://doi.org/10.1542/peds.2008-1406; Jennifer M. Jester et al., *Trajectories of Childhood Aggression and Inattention/Hyperactivity: Differential Effects on Substance Abuse in Adolescence*, 47 J. of THE AM. ACAD. OF CHILD & ADOLESCENT PSYCHIATRY, 1158 (2008), https://doi.org/10.1097/CHI.0b013e3181825a4e; William E. Pelham et al., *The Economic Impact of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents*, 7 AMBULATORY PEDIATRICS : THE OFFICIAL J. OF THE AMBULATORY PEDIATRIC ASSOC., 121 (2007), https://doi.org/10.1016/j.ambp.2006.08.002.

2. Coleen A. Boyle et al., *Trends in the Prevalence of Developmental Disabilities in US Children, 1997-2008* 127 PEDIATRICS 1034 (2008), https://doi.org/10.1542/peds.2010-2989.

3. Laurence Steinberg, *Adolescent Development and Juvenile Justice*, 5 ANN. REV. OF CLINICAL PSYCHOL. 459 (2008), https://doi.org/10.1146/annurev.clinpsy.032408.153603. Sunita Bava & Susan F. Tapert, *Adolescent Brain Development and the Risk For Alcohol and Other Drug Problems*, 20 NEUROPSYCHOLOGY REV. 398 (2010), https://doi.org/10.1007/s11065-010-9146-6; Alexandra O. Cohen & B.J. Casey, *Rewiring Juvenile Justice: The Intersection of Developmental Neuroscience & Legal Policy*, 18 TRENDS IN COGNITIVE SCIENCES 63 (2014), https://doi.org/10.1016/j.tics.2013.11.002.

4. *See* Bava & Tapert, *supra* note 3; *and* Cohen & Casey, *supra* note 3.

sensitivity to rewards, and heightened reactivity to threat and punishment are not uncommon.[5]

It is very likely that these types of developmental trajectories are the result of a mix of genetics and environmental exposure that do not start at the time of the diagnosis or problem behaviors; rather, they start at the earliest periods of life.[6] Early life events, even those occurring before birth, correlate with the ability of children to achieve their full physical, academic and social potential.

II. CHILDHOOD, ADOLESCENT, AND LONG-TERM HEALTH OUTCOMES ARE INFLUENCED BY EARLY MATERNAL AND INFANT MARKERS OF NUTRITION, BIOLOGICAL, AND PSYCHOSOCIAL FACTORS

Maternal influences on neurobiological development during the prenatal period are thought to set the foundation for subsequent developmental processes.[7] These early factors have a sizable impact on physical and mental health.[8]

The theory behind this concept, Developmental Origins of Health and Disease (DOHAD), provides a model for considering the effects of environment on brain/behavior outcomes later in life by integrating decades of research to examine the influence of the early environment on health outcomes.[9] This model incorporates a programming perspective,

5. Alida Benthin et al., *A Psychometric Study of Adolescent Risk Perception*, 16 J. OF ADOLESCENCE 153 (1993), https://doi.org/10.1006/jado.1993.1014; Matthew R.G. Brown et al., *Neural Correlates of High-Risk Behavior Tendencies and Impulsivity in an Emotional Go/NoGo fMRI Task*, 9 FRONTIERS IN SYS. NEUROSCIENCE 24 (2015), https://doi.org/10.3389/fnsys.2015.00024; Michael Dreyfuss et al., *Teens Impulsively React Rather Than Retreat From Threat*, 36 DEVELOPMENTAL NEUROSCIENCE 220 (2014), https://doi.org/10.1159/000357755.

6. Pat Levitt, Pat Levitt & Kathie A. Eagleson, *The Ingredients of Healthy Brain and Child Development*, 57 WASH. U. J.L. & POL'Y 75 (2018).

7. *Id.*; Cynthia Rogers, *Addressing the Psychosocial Risk Factors Affecting the Developing Brain of the High Risk Infant*, 57 WASH. U. J.L. & POL'Y 117 (2018).

8. *See* Levitt, *supra* note 6; *and see* Rogers, *supra* note 7.

9. David J. P. Barker, *Intrauterine Programming of Adult Disease*, 1 MOLECULAR MED. TODAY 418 (1995); David J. P. Barker, *In Utero Programming of Chronic Disease*, 95 CLINICAL SCI. 115 (1998); Simon C. Langley-Evans et al., *Developmental Origins of Health & Disease*, 353 NEW ENGLAND J. OF MED. 1848 (2005), https://doi.org/10.1155/2012/838640; Pathik D. Wadhwa et al., *Developmental Origins of Health and Disease: Brief History of the Approach and Current Focus on Epigenetic Mechanisms*, 27 SEMINARS IN REPRODUCTIVE MED. 358 (2009), https://doi.org/10.1055/s-0029-1237424.Developmental.

whereby salient cues in the early environment guide developmental processes to adapt to expected conditions. For example, work in this area has documented how a mismatch in the pre- versus post-natal environment, specifically with regard to nutritional availability and psychosocial stress, can lead to increased risk for diabetes,[10] coronary heart disease,[11] and changes in brain circuitry.[12] What particularly distinguishes this model is that early exposures are neither "bad" nor "good" agents of development, but rather are cues to the developing brain on what environment to expect at birth. For example, early stress exposure may increase the likelihood that an organism becomes highly stress responsive to later exposures, with attendant consequences for behavioral and somatic health if there is a "mismatch" between the maternal cues and the expectant environments.

The concept of developmental programming represents a guiding theoretical principle in the study of Early Life Stress (ELS) on brain development. This concept suggests that during times of rapid growth, systems are more vulnerable to disorganizing influences.[13] During the prenatal period, brain development proceeds from the basic foundational level of neural tube formation to the migration of neurons, and then to the initial myelination of axons and formation of synapses.[14] Rapid brain development continues during infancy, with frontal and primary sensory

10. Santosh K. Bhargava et al., *Relation of Serial Changes in Childhood Body-Mass Index to Impaired Glucose Tolerance in Young Adulthood*, 350 NEW ENGLAND J. OF MED. 865 (2004).

11. David J.P. Barker et al., *Trajectories Of Growth Among Children Who Have Coronary Events as Adults*, 353 NEW ENGLAND J. OF MED. 1802 (2005), https://doi.org/10.1056/NEJMoa044160; Simon C. Langley-Evans et al., *supra* note 9.

12. Alice M. Graham et al., *Early Life Stress is Associated With Default System Integrity And Emotionality During Infancy*, 56 J. OF CHILD PSYCHOL. AND PSYCHIATRY 1212-22 (2015), https://doi.org/10.1111/jcpp.12409.

13. Claudia Buss et al., *Maternal Cortisol Over the Course of Pregnancy and Subsequent Child Amygdala and Hippocampus Volumes and Affective Problems*, 109 PROCEEDINGS OF THE NAT'L ACADEMY OF SCI. E1312 (2012), https://doi.org/10.1073/pnas.1201295109/-/DCSupplemental.www.pnas.org/cgi/doi/10.1073/pnas.1201295109; Peter D. Gluckman & Mark A. Hanson, *Living With The Past: Evolution, Development, And Patterns Of Disease*, 305 SCI. 1733 (2004), https://doi.org/10.1126/science.1095292; Jonathan R. Seckl, *Glucocorticoids, Developmental "Programming" and the Risk of Affective Dysfunction*, 167 PROGRESS IN BRAIN RES. 17 (2008).

14. Damien Fair & Brad L. Schlaggar, *Brain Development*, *in* ENCYCLOPEDIA OF INFANT AND EARLY CHILDHOOD DEV. 211, (2008); Rhoshel K. Lenroot & Jay N. Gie, *Brain Development in Children and Adolescents: Insights From Anatomical Magnetic Resonance Imaging*, 30 NEUROSCIENCE AND BIOBEHAVIORAL REV. 718 (2006), https://doi.org/10.1016/j.neubiorev.2006.06.001.

cortex showing seventy to eighty percent increases in synaptic density over the first eighteen months of life,[15] and brain volume increasing four-fold from birth to four years of age, accompanied by a rapid decline in the ratio of gray to white matter volume (indicative of increasing myelination).[16] During these periods of rapid change the brain is sensitive to environmental input, which is both necessary for healthy development and potentially harmful depending on factors such as the nature and timing of the input.[17]

III. EARLY LIFE STRESS COMES IN MANY FORMS TO AFFECT BRAIN DEVELOPMENT

ELS influences the development of neurobiological systems implicated in emotional functioning and mental health across the lifespan.[18] Stress is posited to have a particularly pronounced impact during early periods of brain development, both pre- and postnatally, as development occurs rapidly in this window of time, exposing the ongoing formation of brain structural organization to vulnerability.[19] However, as brain-imaging

15. Peter R. Huttenlocher & Arun S. Dabholkar, *Regional Differences in Synaptogenesis in Human Cerebral Cortex*, 387 THE J. OF COMPARATIVE NEUROLOGY 167 (1997).

16. Eric Courchesne et al., *Normal Brain Development and Aging : Quantitative Analysis at in Vivo MR*, 216 NEURORADIOLOGY 672 (2000).

17. Sharon E. Fox et al., *How the Timing and Quality of Early Experiences Influence The Development of Brain Architecture*, 81 CHILD DEV. 28 (2010), https://doi.org/10.1111/j.1467-8624.2009.01380.x; Eric I. Knudsen, *Sensitive Periods in the Development of the Brain and Behavior*, 16 J. OF COGNITIVE NEUROSCIENCE, 1412 (2004), https://doi.org/10.1162/0898929042304796.

18. Camelia E. Hostinar & Megan R. Gunnar, *The Developmental Effects of Early Life Stress: An Overview of Current Theoretical Frameworks, in* CURRENT DIRECTIONS in PSYCHOL. SCI., 22-5, 400-06 (2013), https://doi.org/10.1177/0963721413488889; Michelle M. Loman & Megan R. Gunnar, *Early Experience and the Development of Stress Reactivity and Regulation in Children*, 34(6) NEUROSCIENCE & BIOBEHAVIORAL REV. 867 (2010), https://doi.org/10.1016/j.neubiorev.2009.05.007; M. Sánchez et al., *Early Adverse Experience as a Developmental Risk Factor for Later Psychopathology: Evidence fromRrodent and Primate Models*, 13 DEV. & PSYCHOPATHOLOGY 419 (2001), https://doi.org/10.1016/j.neubiorev.2009.05.007.

19. Claudia Buss et al., *Fetal Programming of Brain Development: Role of Intrauterine Stress and Stress Biology in Susceptibility for Psychopathology* 5 SCI. SIGNALING 245, (2013); Rhoshel K. Lenroot & Jay N. Giedd, *Brain Development in Children and Adolescents: Insights from Anatomical Magnetic Resonance Imaging*, 30 NEUROSCIENCE & BIOBEHAVIORAL REV. 718 (2006), https://doi.org/10.1016/j.neubiorev.2006.06.001; Nim Tottenham & Margaret A. Sheridan, *A Review of Adversity, the Amygdala and the Hippocampus: A Consideration of Developmental Timing*, *in* 3 FRONTIERS IN HUM. NEUROSCIENCE 68, 1-18 (2010), https://doi.org/10.3389/neuro.09.068.2009; *see also* Cynthia Rogers, *Addressing the Psychosocial Risk Factors Affecting the Developing Brain of the*

studies examining the effects of ELS on the brain have predominantly focused on older children and adults,[20] it is difficult to differentiate effects of stress during early developmental periods from the effects of subsequent ongoing adversity, the emergence of coping strategies, or symptoms of psychopathology. Moreover, ELS research has often focused on more extreme sources of adversity, such as institutional rearing,[21] leaving a gap in our understanding of how more mild sources of prenatal and familial stress influence early development of brain systems linked to emotional and mental health.

Research into proximal effects of common forms of stress on brain structure and functioning is beginning to emerge, and has the potential to increase understanding of the vulnerability of the developing brain.[22] For example, findings from a recent functional magnetic resonance imaging (fMRI) study indicate that something as simple as non-physical conflict between parents (interparental conflict) during the first year of life correlates with infants' brain activity in regions thought to be important for processing and regulating stress and emotions. Infants' exposure to higher levels of interparental conflict also correlates with heightened brain reactivity to a stressor-relevant stimulus (e.g., an angry tone of voice) in brain regions that are activated during neutral speech.[23]

High Risk Infant, 57 WASH. U. J.L. & POL'Y 117 (2018).

20. John H. Gilmore et al., *Imaging Structural and Functional Brain Development in Early Childhood*, 19 NATURE REVIEWS NEUROSCIENCE 123 (2018).

21. Nim Tottenham et al., *Prolonged Institutional Rearing Is Associated With Atypically Large Amygdala Volume and Difficulties In Emotion Regulation*, 13 DEV. SCI. 46 (2010), https://doi.org/10.1111/j.1467-7687.2009.00852.x; N. Tottenham et al, *Elevated Amygdala Response to Faces Following Early Deprivation*, 14 DEV. SCI. 190 (2011), https://doi.org/10.1111/j.1467-7687.2010.00971.x.

22. Alice M. Graham et al., *What Sleeping Babies Hear: A Functional MRI Study of Interparental Conflict and Infants' Emotion Processing*, 24 PSYCHOL. SCI. 782-89 (2013), https://doi.org/10.1177/0956797612458803; Jamie L. Hanson et al., *Family Poverty Affects the Rate of Human Infant Brain Growth*, 8 PLOS ONE 12 (2013), https://doi.org/10.1371/journal.pone.0080954.

23. Refers to medial prefrontal cortex (MPFC; rostral anterior cingulate cortex [rACC]) and a subcortical region encompassing the hypothalamus and parts of the thalamus and caudate. Graham et al., *supra* note 22, at 782-89.

IV. ONE BIOLOGICAL INDICATOR OF STRESS OFTEN NEGLECTED AS A STRESS MARKER IS INFLAMMATION

Maternal inflammation during pregnancy is believed to increase risk for offspring neuropsychiatric disorders and adverse physical health outcomes.[24] Strong epidemiological evidence identifies connections between common conditions associated with heightened inflammation during pregnancy, including increased psychosocial stress,[25] but also many other 'stressors,' such as infection,[26] high maternal body mass index (BMI),[27] maternal psychopathology,[28] and more. Indeed, we now know that maternal inflammation, along with its correlate stressors, relates to elevated risk for offspring developing schizophrenia, ASD, ADHD,[29] and other neurological and psychiatric disorders.[30] Thus, maternal

24. Myka L. Estes & A. Kimberley McAllister, *Maternal Immune Activation: Implications for Neuropsychiatric Disorders*, 353 SCI. 772-77 (2016), https://doi.org/10.1126/science.aag3194; Romy Gaillard et al., *Maternal Inflammation During Pregnancy and Childhood Adiposity*, 24 OBESITY 1320-27 (2016), https://doi.org/10.1002/oby.21484; James R. O'Reilly & Rebecca M. Reynolds, *The Risk of Maternal Obesity to the Long-Term Health of the Offspring*, 78 CLINICAL ENDOCRINOLOGY 1, 9-16 (2013), https://doi.org/10.1111/cen.12055.

25. Mary Coussons-Read et al., *Prenatal Stress Alters Cytokine Levels in a Manner That May Endanger Human Pregnancy*, 67 PSYCHOSOMATIC MED. 625-31 (2005), https://doi.org/10.1097/01.psy.0000170331.74960.ad.

26. Alan S. Brown et al., *Serologic Evidence of Prenatal Influenza in the Etiology of Schizophrenia*, *reprinted in* 61 ARCHIVES GEN. PSYCHIATRY 774 (2004), https://doi.org/10.1097/01.ogx.0000151642.60544.d2;; ; ; Urs Meyer et al., *Schizophrenia and Autism: Both Shared and Disorder-Specific Pathogenesis Via Perinatal Inflammation*, *in* 69 PEDIATRIC RES. 5, 26R-33R (2011), https://doi.org/10.1097/MPG.0b013e3181a15ae8.ScreeningIrene Knuesel et *Maternal Immune Activation and Abnormal Brain Development Across CNS Disorders*, 10 NATURE REV. NEUROLOGY 11, 643-60 (2014), https://doi.org/10.1038/nrneurol.2014.187.

27. Paul Krakowiak et al., *Maternal Metabolic Conditions and Risk for Autism and Other Neurodevelopmental Disorders,* 129(5) PEDIATRICS e1121, e1121-28 (2012), https://doi.org/10.1542/peds.2011-2583; Ya-Min Li et al., *Association Between Maternal Obesity and Autism Spectrum Disorder in Offspring: A Meta-analysis,* 46 J. AUTISM DEV. DISORDER 95, 95-102 (2016), https://doi.org/10.1007/s10803-015-2549-8; Lauren C. Reynolds et al., *Maternal Obesity and Increased Risk for Autism and Developmental Delay among Very Preterm Infants*, 34(9) J. PERINATOLOGY 688, 688-92 (2014), https://doi.org/10.1038/jp.2014.80.

28. Rebecca M. Pearson et al., *Maternal Depression During Pregnancy and the Postnatal Period,* 70(12) JAMA PSYCHIATRY 1312, 1312-19 (2013), https://doi.org/10.1001/jamapsychiatry.2013.2163.

29. Johanne T. Instanes et al., *Attention-Deficit/Hyperactivity Disorder in Offspring of Mothers with Inflammatory and Immune System Diseases*, 81(5) BIOLOGICAL PSYCHIATRY 452, 452-59 (2015), https://doi.org/10.1016/j.biopsych.2015.11.024.

30. Knuesel et al., *supra* note 26, at 643-60.

inflammation during pregnancy is a strong candidate for mediating effects of diverse conditions on offspring neurodevelopment with implications for long-term health.

One way to measure the inflammatory state during pregnancy is by measuring what are called cytokines in the blood. Cytokines are inflammatory signaling proteins, and can act as sensors, transducers, and effectors of environmental conditions on the developing embryonic and fetal brain. They can be pro-inflammatory, tending to increase the inflammation, or anti-inflammatory, tending to decrease the inflammatory state. Maternal pro-inflammatory cytokine levels are elevated across a range of diverse high-risk conditions (e.g. infection, high BMI, and psychosocial stress, all of which are sensors)[31] with accompanying increases in pro-inflammatory cytokines in placental tissue, amniotic fluid, and the fetal brain (transducers).[32] Cytokines are also expressed in the fetal brain as part of typical neurodevelopmental processes,[33] and facilitate cellular survival, proliferation and differentiation, neuronal axonal growth and connectivity (i.e., synaptogenesis).[34] Elevated cytokine levels in the

31. John R. Challis et al., *Inflammation and Pregnancy,* 16(2) REPROD. SCI. 206, 206-15 (2009), https://doi.org/10.1177/1933719108329095; Coussons-Read et al., *supra* note 25, at 625-631; Juliette C. Madan et al., *Maternal Obesity and Markers of Inflammation in Pregnancy,* 47 CYTOKINE 61, 61-64 (2009), https://doi.org/10.1016/j.cyto.2009.05.004.

32. Dave A. Gayle et al., *Maternal LPS Induces Cytokines in the Amniotic Fluid and Corticotropin Releasing Hormone in the Fetal Rat Brain*, 286 AM. J. PHYSIOLOGY REG. INTEGRATIVE COMP. PHYSIOLOGY R1024, R1024-29 (2004), https://doi.org/10.1152/ajpregu.00664.2003; Mili Mandal et al., *Maternal Immune Stimulation During Pregnancy Affects Adaptive Immunity in Offspring to Promote Development of TH17 Cells*, 25 BRAIN, BEHAV., AND IMMUNITY 863, 863-71 (2011); https://doi.org/10.1016/j.bbi.2010.09.011; Urs Meyer et al., *The Time of Prenatal Immune Challenge Determines the Specificity of Inflammation-Mediated Brain and Behavioral Pathology*, 26(18) J. NEUROSCIENCE 4752, 4752-62 (2006), https://doi.org/10.1523/JNEUROSCI.0099-06.2006; Ari Urakubo et al., *Prenatal Exposure to Maternal Infection Alters Cytokine Expression in the Placenta, Amniotic Fluid, and Fetal Brain*, 47 SCHIZOPHRENIA RES. 27, 27-36 (2001), https://doi.org/10.1016/S0920-9964(00)00032-3.

33. Ted M. Burns et al., *Developmental Regulation of the Cytokine Expression in the Mouse Brain*, 9 GROWTH FACTORS 253, 253-258 (1993).

34. Lisa M. Boulanger, *Immune proteins in Brain Development and Synaptic Plasticity,* 64 NEURON 93, 93-109 (2009), https://doi.org/10.1016/j.neuron.2009.09.001; Benjamin E. Deverman & Paul H. Patterson, *Cytokines and CNS Development,* 64 NEURON 61, 61-78 (2009), https://doi.org/10.1016/j.neuron.2009.09.002; Mark F. Mehler & John A. Kessler, *Hematolymphopoietic and Inflammatory Cytokines in Neural Development*, 20(8) TRENDS IN NEUROSCIENCES 357, 357-65 (1997), https://doi.org/10.1016/S0166-2236(96)01045-4; Boyu Zhao & Joan P. Schwartz, *Involvement of Cytokines in Normal CNS Development and Neurological Diseases: Recent Progress and Perspectives*, 52 J. NEUROSCIENCE RES. 7, 7-16 (1998),

fetal brain (such as in response to maternal inflammation) trigger alterations in these aspects of neurodevelopment (effectors).[35]

Interleukin-6 (*IL*-6), a pro-inflammatory cytokine,[36] exemplifies this tripartite role. Heightened *IL*-6 concentrations are evident across various maternal gestational conditions (e.g., obesity, psychosocial stress, depression and infection) that, in turn, have been shown to increase susceptibility for psychiatric disorders in offspring.[37] Thus, a significant amount of work has targeted the role of maternal *IL*-6 concentrations in relation to human fetal brain development.[38]

V. THE AMYGDALA IS A KEY BRAIN/LIMBIC STRUCTURE INVOLVED IN MOOD REGULATION AND ANXIETY THAT IS PARTICULARLY VULNERABLE TO EARLY LIFE STRESS

The amygdala is a key limbic structure of the brain nestled in the medial aspect of the temporal lobes and is involved in mood regulation and anxiety.[39] Amygdala structure and function is altered in patients with anxiety and depression.[40] Further, children with ASD show atypical

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https://doi.org/10.1002/(SICI)1097-4547(19980401)52:1<7::AID-JNR2>3.0.CO;2-I.

35. L. Fredrik Jarskog et al., *Cytokine Regulation of Embryonic Rat Dopamine and Serotonin Neuronal Survival in Vitro*, 15(6) INT'L J. DEVELOPMENTAL NEUROSCIENCE 711, 711-16 (1997), https://doi.org/10.1016/S0736-5748(97)00029-4; Yi Pang et al., *IGF-1 Protects Oligodendrocyte Progenitors Against TNFa-Induced Damage by Activation of P13K/Akt and Interruption of the Mitochondrial Apoptotic Pathway*, 55 GLIA 1099, 1099-1107 (2007), https://doi.org/10.1002/glia; Catherine I. Rousset et al., *Maternal Exposure to LPS Induces Hypomyelination in the Internal Capsule and Programmed Cell Death in the Deep Gray Matter in Newborn Rats*, 59(3) PEDIATRIC RES. 428, 428-33 (2006), https://doi.org/10.1203/01.pdr.0000199905.08848.55.

36. Katsuhiko Ishihara & Toshio Hirano, *IL-6 in Autoimmune Disease and Chronic Inflammatory Proliferative Disease*, 13 CYTOKINE & GROWTH FACTOR REVIEWS 357, 357-68 (2002), https://doi.org/10.1016/S1359-6101(02)00027-8.

37. Coussons-Read, *supra* note 25, at 625-631;; Sina Haeri et al., *Do Pregnant Women with Depression Have a Pro-Inflammatory Profile?* 204(1) AM. J. OBSTETRICS AND GYNECOLOGY s322 (Supplement, Jan. 2011), https://doi.org/10.1111/jog.12017; Meyer et al., *supra* note 26, at 26R-33R.

38. Alice M. Graham et al., *Maternal Systematic Interleukin-6 During Pregnancy Is Associated with Newborn Amygdala Phenotypes and Subsequent Behavior at 2 Years of Age*, 83 BIOLOGICAL PSYCHIATRY 109, 109-119 (2017), https://doi.org/10.1016/j.biopsych.2017.05.027.

39. Richard J. Davidson, *Neural and Behavioral Substrates of Mood and Mood Regulation*, 52 BIOLOGICAL PSYCHIATRY 478 (2002).

40. Amit Etkin & Tor D. Wager, *Functional Neuroimaging of Anxiety: A Meta-Analysis of Emotional Processing in PTSD, Social Anxiety Disorder, and Specific Phobia*, 164 AM. J. PSYCHIATRY 1476 (2007), https://doi.org/10.1176/appi.ajp.2007.07030504.

patterns of functional connectivity, and abnormal amygdala growth trajectories have been documented in the disorder.[41] The amygdala is rich in receptors for cortisol, a hormone involved in the neurobiological response to both physiological and psychological stress, and it appears to be particularly vulnerable to the effects of stress exposure during infancy and childhood.[42] Recently, studies also have emerged relating stress in the prenatal environment to amygdala structure and functional connectivity during infancy.[43] Together these studies point to a potential role for alterations in the amygdala as an important pathway through which ELS, beginning prenatally, may influence long term risk for psychiatric disorders. However, this large body of research has not examined the role of inflammation in this pathway.

VI. RECENT EVIDENCE SUGGESTS THAT THE AMYGDALA IS SENSITIVE TO PRENATAL EXPOSURE TO INFLAMMATION

The recent findings of greater right amygdala volume and atypical bilateral amygdala connectivity in the brain[44] have potential implications for offspring susceptibility for psychiatric disorders, either independently, or through altering vulnerability to postnatal environmental influences. Consistent with this interpretation, the newborn amygdala phenotypes associated with higher maternal *IL*-6 concentrations during pregnancy are associated with lower impulse control at twenty-four months of age, a

41. Christine Wu Nordahl et al., *Increased Rate of Amygdala Growth in Children Aged 2 to 4 Years with Autism Spectrum Disorders: A Longitudinal Study*, 69 ARCHIVES GEN. PSYCHIATRY 53 (2012), https://doi.org/10.1001/archgenpsychiatry.2011.145; Phillip Shaw et al., *Childhood Psychiatric Disorders as Anomalies in Neurodevelopmental Trajectories*, 31 HUM. BRAIN MAPPING 917 (2010), https://doi.org/10.1002/hbm.21028; Lucina Uddin et al., *Typical and Atypical Development of Functional Human Brain Networks: Insights from Resting-State FMRI*, FRONTIERS SYS. NEUROSCIENCE, May 21, 2010, at 1, 21, https://doi.org/10.3389/fnsys.2010.00021; Judith S. Verhoeven et al., *Neuroimaging of Autism,* NEURORADIOLOGY, Jan. 2010, at 3, https://doi.org/10.1007/s00234-009-0619-3.

42. Alain Sarrieau et al., *Autodiographic Localization of Glucocoticosteroid and Progesterone Binding Sites in the Human Post-Mortem Brain*, 25 J. OF STEROID BIOCHEMISTRY 717 (1986).

43. Alice M. Graham et al., *The Potential of Infant fMRI Research and the Study of Early Life Stress as a Promising Exemplar*, 12 DEVELOPMENTAL COGNITIVE NEUROSCIENCE 12 (2015), https://doi.org/10.1016/j.dcn.2014.09.005; Dustin Scheinost et al., *Prenatal Stress Alters Amygdala Functional Connectivity in Preterm Neonates*, 12 NEUROIMAGE: CLINICAL 381 (2016), https://doi.org/10.1016/j.nicl.2016.08.010.

44. *See* Buss et al., *supra* note 13.

behavioral phenotype repeatedly linked to difficulties regulating emotions and behaviors at later developmental stages.[45] Furthermore, the newborn amygdala phenotypes mediate an association between higher maternal *IL*-6 concentrations during pregnancy and lower impulse control at two years of age. These data provide support for a pathway from heightened maternal *IL*-6 concentrations during pregnancy to an altered balance between offspring impulsivity and regulatory capacity through alterations in the developing amygdala.

Previous research has identified associations between adversity in early childhood and increased amygdala volume in children.[46] Extending this work to the prenatal environment, Buss and colleagues found an association between higher maternal cortisol concentrations (a stress related hormone) during pregnancy and increased right amygdala volume in school-aged girls, which partially mediated an association between maternal cortisol and child psychiatric symptoms.[47] These most recent findings indicate a potential interaction between the immune system and stress hormones in shaping the developing fetal amygdala. This is consistent with previous findings linking maternal inflammation during pregnancy with increased risk for offspring psychiatric disorders in

45. Angela L. Duckworth et al., *Is It Really Self-Control? Examining the Predictive Power of the Delay of Gratification Task*, 39 PERSONALITY & SOC. PSYCHOL. BULL. 843 (2013), https://doi.org/10.1177/0146167213482589; Sanghag Kim et al., *Effortful Control in "Hot" and "Cool" Tasks Differentially Predicts Children's Behavior Problems*, 41 J. ABNORMAL CHILD PSYCHOL. 43 (2013), https://doi.org/10.1038/jid.2014.371; Liliana J. Lengua et al., *Relations of Growth in Effortful Control to Family Income, Cumulative Risk, and Adjustment in Preschool-age Children*, 43 J. ABNORMAL CHILD PSYCHOL. 705 (2015), https://doi.org/10.1007/s10802-014-9941-2; Hanna Mulder et al., *Psychometric Properties and Convergent and Predictive Validity of an Executive Function Test Battery for Two-Year-Olds*, FRONTIERS PSYCHOL., July 22, 2014, at 1, https://doi.org/10.3389/fpsyg.2014.00733; Julia D. Reuben et al., *Warm Parenting and Effortful Control in Toddlerhood: Independent and Interactive Predictors of School-Age Externalizing Behavior*, 44 J. ABNORMAL CHILD PSYCHOL. 1083 (2016), https://doi.org/10.1007/s10802-015-0096-6.

46. Sonia S. Lupien et al., *Larger Amygdala but No Change in Hippocampal Volume in 10-year-old Children Exposed to Maternal Depressive Symptomatology Since Birth*, 108 PROCEEDINGS NAT'L ACAD. SCI. 14324 (2011), https://doi.org/10.1073/pnas.1105371108/-/DCSupplemental.www.pnas.org/cgi/doi/10.1073/pnas.1105371108; Mitul A. Mehta et al., *Amygdala, Hippocampal and Corpus Callosum Size Following Severe Early Institutional Deprivation: The English and Romanian Adoptees Study Pilot*, 50 J. CHILD PSYCHOL. AND PSYCHIATRY 943 (2009), https://doi.org/10.1111/j.1469-7610.2009.02084.x; Tottenham et al., *supra* note 21, at 46-61; Tottenham & Sheridan, *supra* note 19, at 1-18.

47. Buss et al., *supra* note 13, at E1312–E1319.

humans,[48] and amplified stress reactivity and social deficits in animal models,[49] phenotypes that larger amygdala volumes have been shown to underlie. Variation in maternal *IL*-6 concentrations during pregnancy explained approximately six percent of the variance in right amygdala volume. While this effect may seem modest, it may be clinically meaningful, as suggested by the association between larger right amygdala volume and lower impulse control at age two. Overall, findings are in line with the conceptualization of larger amygdala volume and increased connectivity as indicative of increased risk for subsequent difficulties regulating emotions and behaviors across various stages of development.

CONCLUSION

There continues to be a growing need to understand and combat the impacts of developmental mental health disorders and problem behaviors that occur in childhood, adolescents, and young adulthood. The ability of children to achieve their full physical, academic and social potential is tightly related to early life events. As such, a growing realization that the trajectories that lead to negative outcomes begin at the earliest stages of development—even prior to birth—is transforming the field. The science is now amassed with investigators and research targeting these issues, and recent work highlights the role of ELS (which comes in many forms) and its interaction with biological systems, such as the immune system, in impacting the development of the brain and complex behaviors. Brain regions particularly important for mood regulation, anxiety, and fear, such as the amygdala, appear to be particularly sensitive. However, the brain is

48. Knuesel et al., *supra* note 26, at 643-660; Urs Meyer et al., *Developmental Neuroinflammation and Schizophrenia*, 42 PROGRESS NEURO-PSYCHOPHARMACOLOGY AND BIOLOGICAL PSYCHIATRY 20 (2013), https://doi.org/10.1016/j.pnpbp.2011.11.003; Meyer et al., *supra* note 26, at 26R-33R.

49. Golan Hava et al., *Alterations in Behavior in Adult Offspring Mice Following Maternal Inflammation During Pregnancy*, 48 DEVELOPMENTAL PSYCHOBIOLOGY 162-168 (2006), https://doi.org/10.1002/dev.20116; Urs Meyer et al., *supra* note 32, at 4752–4762; A. Sasaki et al., *Perinatal High Fat Diet Alters Glucocorticoid Signaling and Anxiety Behavior in Adulthood*, 240 NEUROSCIENCE 1, https://doi.org/10.1016/j.neuroscience.2013.02.044; Elinor L. Sullivan et al., *Chronic Consumption of a High-Fat Diet During Pregnancy Causes Perturbations in the Serotonergic System and Increased Anxiety-Like Behavior in Nonhuman Primate Offspring*, 30 J. NEUROSCIENCE 3826 (2010), https://doi.org/10.1523/JNEUROSCI.5560-09.2010.

a complex system with billions of neurons and anywhere from 100-1000 trillion connections. Hence, while the work goes on, a complete understanding of the interactions between ELS, environment, brain, and behavior will continue to be a significant challenge in years to come.