Under the Skin: Summarizing Existing Research on Physiological Variables behind Disruptive Behavior Disorders and Their Response to Treatment.

Andrea D. Guastello, PhD[1]
Melanie Nelson, PhD[1]
Brittany Bailey, MS[1]
Brian Olsen, PhD[1,2]
[1]University of Florida, Gainesville, Florida; [2]St. Luke's Hospital, Twin Falls, Idaho

Key Words: hypothalamic-pituitary-adrenal axis, sympathetic nervous system, cortisol, salivary alpha-amylase, heart rate, vagal tone, childhood disruptive behavior disorders

Abstract: Clinicians are often trained to conceptualize cases from a biopsychosocial model, though many of us receive considerably less training and continuing education in the biological variables related to the disorders we treat. This research brief will summarize the existing literature related to the hypothalamic-pituitary-adrenal axis functioning and sympathetic nervous system functioning in children with disruptive behavior disorders with special focus on children age 2 to 7. Additionally, the available studies examining the change in these variables over the course of behavioral interventions for disruptive behaviors will be included. Clinicians will benefit from an increased understanding of biological processes underlying disruptive behaviors, allowing them to improve their case conceptualizations and the psychoeducation they can provide caregivers. Moreover, though the current research is still working toward identifying a biomarker for disruptive behaviors, this research brief will explain the rationale behind biomarkers in psychological treatment and the current research in this area. Next steps for research in this growing subfield will also be discussed.

Background

The Major Systems: The stress system includes neuroanatomical and functional structures that work together to maintain homeostasis through behavioral, physiological, and biochemical changes (Angeli et al., 2018, Chrousos, 2009). The hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system (SNS) are the actors of the stress system and are responsible for secretion of glucocorticoids and catecholamines respectively (Chrousos & Pervanidou, 2014). There is growing evidence that dysregulation of these systems is related to various psychological conditions. In fact, this system is commonly associated with stress, and over activity of the HPA axis and SNS has been studied frequently in the context of anxiety disorders (Nikolic et al., 2018). However, there is growing evidence that dysregulation of the system can also contribute to other psychological conditions. In children, disruption of the HPA axis and SNS is associated with childhood disruptive behavior disorders (e.g., Oppositional Defiant Disorder, Conduct Disorder; Stadler et al., 2008; Schoorl et al., 2016). Additionally, there is growing evidence that hypoactivity (under activity) of the HPA axis is associated with the impulsivity and lack of inhibition associated with Attention Deficit Hyperactivity Disorder (ADHD) (Angeli et al., 2018).

Measuring HPA Functioning: Cortisol has long been understood as a glucocorticoid (steroid hormone) produced by the adrenal glands and released to regulate the stress system (Hatfield & Williford, 2017). Generally, increased levels of cortisol indicate greater activity of the HPA system, while decreased level of cortisol indicated less activity of the HPA system. However, cortisol levels also vary based on time of day, with highest levels of cortisol being measured thirty minutes after awakening in the morning and gradual decline throughout the day (Gunnar & Donzella, 2002). Cortisol can be measured by either blood samples or salvia samples, and salivary cortisol is strongly correlated with serum (blood) cortisol (Charmandari et al., 2005). Consequently, saliva samples are used more frequently in research because they are less invasive and avoid the potential confound of the stress of the blood draw increasing levels of cortisol (Katz & Peckins, 2017).

Measuring SNS Functioning: The autonomic nervous system is comprised of two interconnected systems: the sympathetic nervous system (fight or flight response) and the parasympathetic nervous system (responsible for recovery and rest). Under stress, the body typically responds with activation of the sympathetic nervous system and withdrawal of the parasympathetic nervous system. The sympathetic nervous system (SNS) is responsible for several physiological changes when activated including increased heart rate and increased saliva production. Heart rate is a straight forward and noninvasive measure of SNS activity and improved technology makes measurement in clinical settings more feasible than ever before. Conversely, cardiac vagal tone represents the contribution of the parasympathetic nervous system to cardiac regulation. To noninvasively assess vagal tone, researchers measure respiratory sinus arrhythmia (RSA), which is a component of heart rate variability. In stressful situations, healthy individuals show a withdrawal or suppression of RSA leading to increased heart rate and improved ability to cope with the stressful situation (Graziano et al., 2012). Finally, the salivary enzyme alpha-amylase (sAA), has been documented to be sensitive to psychosocial stress and has been used as a biomarker to reflect activity in the SNS (Nater & Rohleder, 2009). Under stress, the adrenal cortex increases saliva production, leading the salivary glands to secrete sAA (Chaturvedi et al., 2018). Greater levels of sAA indicated greater activity in the SNS, while lower levels indicate less activity. Because it does not appear to be highly related to cortisol, sAA has been used as an additional parameter in the measurement of stress (Nater et al., 2006).

Problem Statement

There is a growing body of research indicating that there are physiological and neurobiological differences in children with disruptive behavior disorders (e.g., Oppositional Defiant Disorder (ODD), Conduct Disorder (CD), and Attention Deficit Hyperactivity Disorder (ADHD)). More specifically, hypoactivity of the stress system has been measured in several clinical samples and is likely related to difficulties with inhibition and lack of response to environmental consequences leading to the development of disruptive behavior disorders. Understanding what is happening internally for these children has important implications for understanding the mechanisms of change in our current behavioral treatments. It may also help clinicians to understand why some individuals do not respond to treatment, allowing for treatment modifications to reach these individuals.

Differences in Heart Rate: Meta-analyses have found that decreased autonomic arousal as measured by low resting heart rate is associated with aggressive behavior in children and adolescents (Lorber, 2004; Ortiz & Raine, 2004). Consequently, researchers have concluded that low resting heart rate is the best replicated biological correlate of aggressive and antisocial behavior in children and adolescents, reflecting a fearless personality that is unresponsive to the social context (Stradler et al., 2008). Low resting heart rate has even been found to be predictive of later criminal behavior (Raine, Venables, & Willimas, 1990).

Differences in Heart Rate Variability: Vagal tone, which is related to heart rate variability is also linked with psychological variables like self-regulation (Laborde, Mosley & Thayer et al., 2017). Young children with greater levels of RSA withdrawal or suppression (greater heart rate variability) display better self-regulation and active coping skills, social competence, sustained attention, and fewer behavior problems (Graziano et al., 2012). More specifically, there is an inverse relationship between heart rate variability and scores on the CBCL Externalizing Scale (Pine et al., 1998). This association can even be observed in neonates, as one study found that higher heart rate variability of very low-birth-weight preterm neonates was associated with fewer behavior problems at 3 years old (Doussard-Roosevelt, Porges, & McCleeny, 1996). Conversely, low baseline RSA in preterm neonates predicted greater prevalence of behavior problems at 5 years (Feldman, 2009).

Differences in the HPA Axis: Hypoactivity of the HPA axis has also been documented in externalizing problems such as ODD and CD (Snoek et al., 2004; Van Goozen & Fairchild, 2008). For instance, Van de Wiel et al. (2004) found that low cortisol reactivity to stress was predictive of higher levels of aggression behavior in school-aged boys in treatment of ODD/CD. Additionally, Blair et al. (2005) discovered blunted cortisol reactivity among highly aggressive preschoolers form low-income families.

Differences Specific to ADHD: Recent studies have also started to explore the role of the stress system in ADHD. Several studies have documented hypoactivity of the HPA system in ADHD (Isaksson et al., 2012; Ma et al., 2011; McCarthy et al., 2011; King et al., 1998). Specifically, Angeli et al. (2018) found that children with ADHD had significantly lower levels of salivary cortisol at two time points (30 minutes after awakening at 6p.m.) compared to healthy controls, and that children with ADHD had lower overall cortisol secretion over a 24 hour period. However, SNS basal activity as measured by sAA was not affected by the presence of ADHD in their sample. Similarly, Stadler et al. (2008) found that children with high or low heart rates did not differ in regard to the reduction of attention problems following a parent-training intervention.

Solutions

Relationship to Treatment Outcomes: Schoorl et al., (2017) found that in a study of children and parents undergoing behavioral intervention for ODD/CD children with more pronounced cortisol stress responses and better cortisol recovery demonstrated a greater reduction in aggression over time. That is to say that, boys with ODD/CD who responded less well to stress and who recovered less well after stress showed less reduction in aggression over the course of the 6-months of treatment and at 1-year follow-up. Therefore, lower cortisol reactivity is likely correlated with a worse prognosis for aggressive behaviors. The finding from Schoorl et al., (2017) was consistent with Van de Wiel et al., (2004) who found that children with low cortisol levels during stress had more problem behaviors after 9 months of treatment than children with disruptive behavior disorders who did show a cortisol response to stress.

Regarding heart rate, it appears that children with lower heart rates are less likely to profit from therapy (Stadler et al., 2008). Stadler et al. (2008) completed a parent training based intervention study for children with disruptive behavior disorders and found that children with higher heart rates experienced a greater decline in aggressive behavior compared to less aroused children in their study. Additionally, children with lower levels of pre-treatment RSA suppression (lower heart rate variability) took longer to complete Parent Child Interaction Therapy (Graziano et al., 2012).

Changes in Physiological Variables following Behavioral Treatment: Evidence is accruing that psychosocial interventions can have normalizing effects on the dysregulated functioning of the stress system. Hatfield and Williford (2017) found that at the end of a school year, children whose teacher participated in a teacher-child relationship-focused intervention displayed a change in cortisol across the morning compared to children whose were assigned to the business as usual condition. Additionally, Brotman et al. (2007) found that children who underwent a family-based preventative intervention for children at high risk for antisocial behavior demonstrated normalized stress responses at posttreatment. These results were consistent with later findings by O’Neal et al. (2010) that children in an early family intervention for preschoolers at risk for antisocial behavior demonstrated increased cortisol levels, and that cortisol levels acted as a mediator between intervention or control placement and decreases in aggressive behavior. Moreover, children born premature are at greater risk for dysfunction in the stress system. In a study of premature children, a mother-child relationship with low levels of hostility, high levels of positive behaviors, and low levels of dysfunctional interactions predicted improvements in the RSA suppression for children born premature from age 2 to 5.5 (Calkins, 2008).

Regarding PCIT specifically, Graziano et al., 2012 conducted a PCIT intervention for parents of children who were born prematurely. They found that parents’ improvement in the use of “do skills” post-treatment was positively associated with post-treatment improvements in RSA suppression. However, they did not find a relationship between decreases in the parental use of “don’t skills” and the children’s physiological regulation. Consequently, they concluded that high use of positive parenting behaviors buffers the impact of negative parenting behaviors on physiological regulation. This finding was consistent with a previous case study that found that PCIT improved parasympathetic control and improved emotion regulation in a child born premature (Banger et al., 2009) and is also consistent with the conclusion from O’Neal et al. (2010) that parental warmth is important for the development of a healthy cortisol response in early childhood.

Conclusions and Recommendations

There appears to be ample evidence that neurobiological and physiological differences contribute to the development and maintenance of disruptive behavior disorders in children. However, the research is still too limited for these findings to have far reaching clinical utility. At this stage in the research, it appears that children with hypoactive stress systems as evidenced by low heart rate, low heart rate variability, and low cortisol levels are at increased risk of developing and maintaining a behavior disorder. Additionally, cortisol levels appear to be lower in children with ADHD, though differences in heart rate and sAA have not been observed in ADHD. As technology improves, the ability to measure physiological variables becomes less invasive and less expensive. Therefore, clinician-scientists are highly encouraged to consider adding physiological variables to their studies. One difficulty with the current body of literature is that studies may only investigate one physiological variable at a time making comparison across studies more difficult. Whenever possible, researchers are encouraged to measure multiple physiological variables at once.

Currently, there is a need for more baseline and treatment outcomes studies. Findings have not been replicated enough for conclusions to be drawn about which biomarkers are the best predictors of behavioral disorders and ideally future research would aim to create reference values that can be used by clinicians. Additionally, more intervention studies are needed to determine how physiological variables impact the course of treatment and how they change during treatment. The good news is that initial findings do indicate that psychosocial interventions can have positive influences on a child's underlying physiology and that dysfunctional stress responses can be normalized. These findings have tremendous impact on understanding the neurobiological mechanisms behind the behavior change we see in treatment. One difficulty with the current intervention studies is that many studies use different intervention protocols. While several have used parent or teacher skills focused interventions, they are still not directly comparable. PCIT as a well-established, manualized, and consistently delivered intervention is well suited to be used in these studies. Specifically, Graziano et al. (2012) advocate for future research to examine the effect of PCIT on specific sympathetic linked cardiac activity and cortisol reactivity.

As the literature base expands and is disseminated, the eventual hope is to integrate physiological measures with traditional behavior rating scales in the initial assessment and treatment of children with behavior disorders. Eventually, a clinician will be able to use objective measures like heart rate and cortisol in concert with parent and teacher report measures to determine if a child is a risk for a behavioral disorder and if they should receive behavioral, pharmacological, or combined treatment. For instance, Schoorl et al. (2017) recommend that children demonstrating biological risk profiles might be better treated with psychopharmacological interventions to alter the biological stress system than by psychotherapeutic interventions (e.g., parent training) alone. Additionally, better understanding of the relationships among the stress system, child behavior, and the child environment may help parents develop more buy-in for behavioral or pharmacological treatments.

Citations

1. Angeli, E., Korpa, T., Johnson, E.O., Apostolakou, F., Papassotiriou, I., Chrousos, G.P., Pervanidou, P. (2018). Salivary cortisol and alpha-amylase diurnal profiles and stress reactivity in children with Attention Deficit Hyperactivity Disorder. *Psychoneuroendocrinology, 90*, 174-181.
2. Bagner, D.M., Sheinkopft, S.J., Miller-Loncar, C.L., Vohr, B.R., Hinckley, M., Eyeberg, S.M., & Lester, B.M. (2009) Parent-Child Interaction Therapy for children born premature: A case study and illustration of vagal tone as a physiological measure of treatment outcome. *Cognitive and Behavioral Practice, 16*, 468-477.
3. Blair, C. Granger, D., & Razza, R.P. (2005). Cortisol reactivity is positively related to executive function in preschool children attending Head Start. *Child Development, 76,* 554-567.
4. Brotman, L.M., Gouley, K.K., Huang, K.Y., Kamboukos, D., Fratto, C., & Pine, D.S. (2007). Effects of a psychosocial family-based preventive intervention on cortisol response to a social challenge in preschoolers at high risk for antisocial behavior. *Archives of General Psychiatry, 64,* 1172-1179.
5. Calkins, S. Graziano, P., Berdan, L., Keane, S., & Degnan, K (2008). Predicting cardiac vagal regulation in early childhood from maternal-child relationship quality during toddlerhood. *Developmental Psychobiology, 50*, 751-766.
6. Charmandari, E.. Tsigos, C., & Chrousos, G. (2005) Endocrinology of the stress response. *Annual Review of Physiology, 67*, 259-284.
7. Chatruvedi, Y., Chaturvedy, A., Marwah, N., Chaturvedi, S., Agarwal, S., & Agarwal, N, (2018). Salivary cortisol and alpha-amylase: Biomarkers of stress in children undergoing extraction: An *in vivo* study. *International Journal of Clinical Pediatric Dentistry, 11(3),* 214-218.
8. Chrousos, G.P. (2009). Stress and disorders of the stress system. *Nature Reviews Endocrinology, 5,* 374-381.
9. Chrousos, G.P. & Pervanidou, P. (2014). Stress and endocrine physiology. *Reference Module in Biomedical Sciences, 4,* 325-332.
10. Doussard-Roosevelt, J.A., Porges, S.W., & McCleeny, B.D. (1996). Behavioral sleep states in very low birth weight preterm neonates: Relation to neonatal health and vagal maturation. *Journal of Pediatric Psychology, 21*, 785-802.
11. Feldman, R. (2009). The development of regulatory functions from birth to 5 years: Insights from premature infants. *Child Development, 80,* 544-561.
12. Graziano, P.A., Bagner, D.M., Sheinkopf, S.J., Vohr, B.R., & Lester, B.M. (2012). Evidence-based intervention for young children born premature: Preliminary evidence for associated changes in physiological regulation. *Infant Behavior and Development, 35*, 417-428.
13. Gunnar, M.R., & Donzella, B. (2002). Social regulation of the cortisol levels in early human development. *Psychoneuroendocrinology, 27*, 199-220.
14. Hatfiled, B.E. & Williford, A.P. (2017). Cortisol patterns for young children displaying disruptive behavior: Links to a teacher-child, relationship-focused intervention. *Prevention Science, 18,* 40-49.
15. Isaksson, J., Nilsson, K.W., Nyberg, F., Hogmark, A., & Lindbald, F. (2012). Corisol levels in children with Attention-Deficit/Hyperactivity Disorder. *Journal of Psychiatric Research, 46*, 1398-1405.
16. Katz, D.Z. & Peckins, M.K. (2017). Cortisol and salivary alpha-amylase trajectories following a group social-evaluative stressor with adolescents. *Psychoneuroendocrinology, 86*, 8016.
17. King, J.A., Barkley, R.A., & Barrett, S. (1998). Attention-deficit hyperactivity disorder and the stress response. *Biological Psychiatry, 44,* 72-74.

18. Laborde, S. Mosley, E., & Thayer, J.F. (2017). Heart rate variability and cardiac vagal tone in psychophysiological research – recommendations for experiment planning, data analysis, and data reporting. *Frontiers in Psychology, 8,* 213.
19. Lober, M.F. (2004). Psychophysiology of aggression, psychopathy, and conduct problems: a meta-analysis. *Psychological Bulletin, 130*, 531-552.
20. Ma, L., Chen, Y.H., Liu, Y.Y., Wang, Y.X. (2011). The function of hypothalamus-pituitary-adrenal axis in children with ADHD. *Brain Research, 1368*, 159-162.
21. McCarthy, A.M., Hanrahn, K., Scott, L.M., Zemblidge, N., Kleiber, C., Zimmerman, M.B., (2011). Salivary cortisol responsivity to an intravenous catheter insertion in children with attention-deficit hyperactivity disorder. *Journal of Pediatric Psychology, 36*, 902-910.
22. Nater, U.M., La Marca, R., Florin, L., Moses, A., Langhans, W., Koller, M.M., & Ehlert, U. (2006). Stress-induced changes in human salivary alpha-amylase activity-associations with adrenergic activity. *Psychoneuroendocrinology, 31*, 49-58.
23. Nater, U.M., & Rohleder, N. (2009). Salivary alpha-amylase as a non-invasive biomarker for the sympathetic nervous system: Current state of research. *Psychoneuroendocrinology, 34*, 486-496.
24. O'Neal, C.R., Brotman, L.M., Huang, K.Y., Gouley, K.K., Kamboukous, D., Calzada, E.J., & Pine, D.S. (2010). Understanding relations among early family environment, cortisol response, and child aggression via a prevention experiment. *Child Development, 81(1),* 290-305.
25. Ortiz, J. & Raine, A. (2004). Heart rate level and antisocial behavior in children and adolescents: A meta-analysis. *Journal of the American Academy of Child Adolescent Psychiatry, 43,* 154-162.
26. Pine, D.S., Wasserman, G.A., Miller, L., Coplan, J.D., Bagiella, E., Kovelenku, P., et al. (1998). Heart period variability and psychopathology in urban boys at risk for delinquency. *Psychophysiology, 35,* 521-529.
27. Raine, A., Venables, P.H., & Williams, M (1990). Relationships between central and autonomic measures of arousal at age 15 years and criminality at age 24 years. *Archives of General Psychiatry, 47,* 1003-1007.
28. Schoorl, J., Rijn, S.V., Weid, M.D., Goozen, S.H.M.V., & Swaab, H. (2017). Neurobiological stress responses predict aggression in boys with oppositional defiant disorder/conduct disorder: a 1-year follow-up intervention study. *European Child and Adolescent Psychiatry, 26,* 805-813.
29. Snoek, H., Van Goozen, S.H.M. Matthys, W., Buitelaar, J.K., Van Engeland, H. (2004). Stress responsivity in children with externalizing behavior disorders. *Developmental Psychopathology, 16*, 389-406.
30. Stadler, C., Grasmann, D., Fegert, J.M., Holtmann, M., Poustka, F., & Schmeck, K. (2008). Heart rate and treatment effect in children with disruptive behavior disorders. *Child Psychiatry and Human Development, 39(3*), 299-309.
31. Van de Wiel, N.M., Van Goozen, S.H.M., Matthys, W., Snoek, H., & Van Engeland, H. (2004). Cortisol and treatment effect in children with disruptive behavior disorders: a preliminary study. *Journal of Clinical Child Adolescent Psychology, 43*, 1001-1018.
32. Van Goozen S.H.M., & Fairchild, G. (2008). How can the study of biological processes help design new interventions for children with severe antisocial behavior? *Developmental Psychopathology, 20*, 941-973.