VAGUS NERVE STIMULATION FOR REACTIVE ATTACHMENT DISORDER

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Abstract

Reactive Attachment Disorder (RAD) is a potential consequence of pervasive neglectful and unpredictable caregiving behaviors, and has extensive psychological and daunting consequences on the vulnerable and developing young brain. Current treatment strategies for RAD are conspicuously lacking, relying on indiscriminately targeted psychopharmacological therapies with pharmacokinetic and pharmacodynamic complications due to developmental vulnerabilities, and the unavailability of evidence based psychotherapeutic interventions. At present, there is an acute demand for innovative research into more developmentally sensitive and neurobiologically targeted treatment strategies for this population, and as a result, Vagus Nerve Stimulation (VNS) is being proposed as a potentially efficacious treatment for children with RAD due to the targeted effects on limbic system structures and neurotransmitter systems that are directly implicated in the neurobiology of RAD. Rationale for the use of VNS in the pediatric RAD population is based upon evidence from the safety and efficacy of VNS in the pediatric epileptic population, in conjunction with the fairly consistent observed anxiolytic and mood stabilizing effects reported in multiple clinical studies.

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CHAPTER 1. INTRODUCTION

Problem Identification

Reactive attachment disorder (RAD) is one possible psychological consequence of early childhood maltreatment for young children (Hornor, 2008), and is described by the DSM-IV-TR as markedly disturbed and developmentally inappropriate social relatedness usually beginning before age 5, and is the direct result of pathogenic care (APA, 2000). The central deficit in RAD is the child's inability to develop healthy attachment to a caregiver, and the etiology is presumed to be a result of pervasive neglectful and unpredictable care giving behaviors (Boekamp, 2008). Traditional attachment theory postulates that infants are biologically predisposed to form attachments to available adult caregivers (Dykas & Cassidy, 2011), and consequences will reverberate throughout the developing years in the event this does not occur.

Current stress research suggests that the infant and child's capacity to cope with stress is correlated with deprivation of parental care-giving behaviors, and presents a source of stressful environmental information for the early developing brain (Nelson, Bos, Gunnar & Sonuga-Barke, 2011).

Recent studies have added to the evidence that childhood maltreatment is associated with morphological brain alterations, and pre-clinical studies have previously shown that childhood maltreatment can result in morphological changes in brain structure (Chaney, et al., 2014). Structural changes in the hippocampus, prefrontal cortex, corpus callosum and amygdala (Spinelli, et al., 2009) are associated with long term arousal of the neurochemical and biological stress systems. These areas of the brain have received

particular attention in studies of the neural correlates of childhood maltreatment (Belsky & De Haan, 2011; Teicher, Tomoda & Anderson, 2006).

To date, there are no current evidence-based interventions for children with attachment disordered behaviors (Boekamp, 2008; O'Connor & Zeanah, 2003), and there are no randomized clinical trials to date designed to evaluate the utility of a treatment specifically targeting RAD (Buckner, Lopez, Dunkel & Joiner, 2008). Adding to these complexities, many current treatment approaches that are utilized are not systematic, or even theoretically coherent (Marvin & Whelan, 2003), and not much is known about the long-term effects of these interventions (Kalinauskiene, et al. 2009).

In regard to psychotropic mediations, there are no current psychopharmacological intervention trials for RAD (Boris & Zeanah, 2005; NIMH, 2012), and there is no literature supporting the use of pharmacological treatment to address the core attachment deficit (Weibnerg, 2009) seen in RAD. Additionally, there is an overall limited evidence base for efficacy of psychotropic medications in children (AACP, 2012).

Much of the published clinical trial findings applied to children and adolescents have been extrapolated from single-agent versus placebo drug trials using adult patients while measuring acute and short-term outcomes (Magellan Health Services, 2013). Results from adult studies being extrapolated to children is not necessarily appropriate because of developmental differences in pharmacokinetics (what the body does to the drug) and pharmacodynamics (what the drug does to the body) (Sadock & Sadock, 2009). Difficulties arise in the form of medication side effects when systemically administered psychotropics are transported via cerebral circulation, cross the blood-brain barrier, and

in turn effect neuronal excitation and inhibition in areas of normal brain function (Labar & Dean, 2002).

Typically, RAD follows a continuous course and the symptoms persist even when a child is able to develop appropriate attachments (Glaser, 2000), resulting in significant negative impact on foster children's placement and permanency outcomes (Leathers, Spielfogel, Gleeson & Rolock, 2012).

Epidemiology and Etiology

In the U.S in 2012, more than 3.8 million children were the subjects of at least one report of abuse or neglect, and 17.7% of the children were found to be victims with dispositions of substantiation. With the exception of sexual abuse, victims in the age group of 1 to 2 years (11.8% and 11.9%) had the largest percentages across all maltreatment types, and the ages of 3-4 (11.6% and 11.0%) had the next largest percentages across all maltreatment types (National Child Abuse and Neglect Data Systems [NCANDS], 2012). The trend of these numbers between 2008 and 2012 do not show any changes and the current estimated annual national cost of child abuse and neglect exceeded $100 billion during that year (Sugaya, et al. 2012).

Despite decades of research, there is little consensus about how to prevent maltreatment, provide intervention for victims, and ameliorate its possibly lifelong consequences (Twardosz & Lutzker, 2010). There is no single risk factor or set of risk factors that have emerged in the literature which provides a sufficient cause of maltreatment, though a number of etiological models have evolved that consider a

combination of individual, familial, and environmental factors that may contribute to the occurrence of child maltreatment (Cicchetti & Toth, 2005).

A high prevalence of behavior problems is found among foster children who have experienced abuse and/or neglect, and these behavioral problems have significant negative impact on foster children's placement and permanency outcomes (Leathers, Spielfogel, Gleeson & Rolock, 2012). In support of this, as of 2012, the number of children in foster care was 400,540, and the number of children who were adopted with public child welfare involvement was only 50,516 (U.S Children's Bureau, 2013). Very little is known about the percentage of parents willing to foster children with emotional or behavioral problems, but available research suggests that the majority of parents are not willing to foster children with such problems (Cox, et al. 2011).

To date, there are no data sets on the types of behavioral disorders or psychiatric disorders that children present with in foster care or when adopted. There is, however, research that indicates that children being raised in the foster care system are considered to be at risk of developing RAD. The research also indicates that an adopted child may have more psychological and behavioral issues and also be more at risk of a diagnosis of RAD than a child raised by a biological parent (Stinehart, et al. 2012).

According to literature, there are limited to no prevalence estimates for RAD, it is one of the least researched disorders in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR), and little is known about the course of the disorder (APA, 2000; Lake, 2005; Chaffin, et al., 2006).

Rationale

In an effort to develop an evidence-based treatment for RAD, brain stimulation modalities have been reviewed and considered for further study as potentially efficacious treatment interventions for this disorder in children 5-7 years of age.

The age at which neural plasticity is highly accessible in young children is seven years of age and younger (Delima & Vimpani, 2011; Perry, 2009; Johnson, 2009), the mean age for which children are adopted in the U.S is 6.4 (U.S Children's Bureau, 2013), and RAD symptoms begin before age 5 (APA, 2000). These ages are within the critical time period as being the most vulnerable (Heim & Binder, 2011).

Moreover, there are no current empirically supported treatments for RAD (Boekamp, 2008; O'Connor & Zeanah, 2003), there are no current psychopharmacological treatments indicated for RAD (National Institute of Mental Health [NIMH], 2012), RAD is one of the top five health problems with children who are adopted internationally (Steinhart, et al., 2012), and early childhood maltreatment predicts negative affective, somatic and behavioral outcomes both in childhood and adulthood in a linear fashion (Johnson-Reid, Kohl & Drake, 2012). In addition, these age ranges are the earliest phase of development where a child could be assessed and have the capacity to understand what is asked of them (Delima & Vimpani, 2011).

Hypothesis

The above are all pivotal factors in the rationale for attempting to demonstrate that a targeted brain-based intervention would be potentially efficacious during these stages of neurological development.

Upon a critical review of all of the available literature on several brain stimulation modalities, all besides VNS were entirely excluded. Some of the reasons include the potential for severe and possible lasting side effects, increased level of surgical invasiveness, level of physical and emotional discomfort during administration, little or no studies of use in the pediatric or adolescent populations, significant stigma, irreversibility of brain lesions, and negligible understanding regarding the potential biological targets of the intervention(s), or indiscriminate biological targeting rendering it not applicable to the underlying substrates of RAD.

VNS is the only brain stimulation modality being suggested as a potential intervention for children between the ages of 5-7 years who have RAD. The predominant rationale being that there have already been a significant amount of controlled clinical studies and trials that have been conducted utilizing the VNS device within the infant and pediatric populations (1.4 years of age through the pre-adolescent stage) for the treatment of treatment refractory epilepsy (Yu, et al., 2014). Moreover, these studies have indicated that the use of VNS in the pediatric epileptic population is safe and effective, with transient, minor and tolerable side effects, if any at all (Morris III, et al., 2013; Awaad, Rizk, Roosen, Mcintosh & Waines, 2011).

VNS is postulated to have projective effects on limbic system structures, in conjunction with direct effects on specific neurotransmitter systems involved in anxiety (norepinephrine) and mood modulation (serotonin)(George, Rush, Sackeim & Marangell, 2003; Conway, et al. 2012). Additionally, VNS has the ability to excite or inhibit neuronal activity, thus affecting the neurotransmitter concentration in different regions of

the brain (Albert, et al. 2009). These putative mechanisms of action would have direct effects on specific regions of the brain and neurotransmitters that are directly implicated in the neurobiology of RAD.

Based on the safety and efficacy of VNS in the pediatric epileptic population for the treatment of epilepsy, in conjunction with the fairly consistent observed mood and anxiety improvements in this population being treated with VNS, and potential targeted brain regions that regulate mood and anxiety (Fitzgerald, 2011; Malhi, et al. 2006) VNS is being suggested in the RAD pediatric population.

Despite the fact that there is an obvious need for further research in this area, there is obligation as a scientific community, and to the larger community at hand, to not only focus on treating the symptoms, but to understand the etiology of the neurobiological aspects of this disorder and move toward more effective, regionally targeted, scientifically based interventions with the least amount of deleterious side effects. This study will specifically address the theoretical, neurodevelopmental and neurobiological underpinnings of RAD and propose that VNS may be effective treatment intervention for children with RAD between 5-7 years of age.

CHAPTER 2. LITERATURE REVIEW

The purpose of this chapter is to review the literature on attachment theory and the supporting evidence from neuropsychology regarding the neurobiological effects of early childhood maltreatment. This literature review will provide a rational that RAD should be viewed concomitantly from the basic principles suggested by attachment theory, evidence from developmental neuropsychology and the diathesis-stress model. The implications of attachment will be discussed from all of the above mechanisms in conjunction with how these mechanisms co-act, followed by a critical review of recent research in brain stimulation techniques. Finally, current therapeutic and psychopharmacological interventions for RAD will be discussed.

Definition of Childhood Maltreatment and Early Life Stress

Child maltreatment occurs in several different forms. Commonly studied early childhood maltreatment and stressors include physical, sexual, emotional and verbal abuse, neglect, social deprivation, disaster, and household dysfunctions, including witnessing of violence, criminal activity, parental separation, parental death or illness, poverty and substance abuse (Pechtel & Pizzagalli, 2011).

Under the umbrella of early life stress includes child abuse and neglect, which is a wo(man) made phenomena that is defined under Federal legislation (U.S Department of Health, 2010) to be, “Any recent act or failure to act on the part of a parent or caregiver which results in serious physical or emotional harm, sexual abuse or exploitation”, or, “An act or failure to act which presents an imminent risk of serious harm”.

The U.S Department of Health and Human Services, Administration on Children, Youth and Families (2007) defines the different forms of child maltreatment within a commission-omission paradigm. Physical and sexual abuse are acts of commission of excessive physical punishment and inappropriate sexual contact with a child, respectively, whereas neglect is an act of omission, with harmful effects resulting from the lack of a caregiver's actions for a child's welfare. Exposure to domestic violence diverges from the commission-omission definitional schema for child maltreatment in that the action is directed to someone other than the child, but is nonetheless resultantly harmful to the child's welfare.

Specifics regarding exactly what types of experiences (abuse or neglect) will not be deciphered in the definition used for this paper. Questions still remain about the conditions necessary for RAD to develop (Gleason, et al. 2011), and dimensions of parental behavior are complex and maltreatment can vary by levels of severity, types of maltreatment, and types of episodes (Baer & Martinez, 2006).

A reliable and valid system for defining, measuring, and classifying types of maltreatment has not yet been developed (Twardoz & Lutzker, 2010). Furthermore, it is common for children to experience multiple forms of maltreatment (Wilson, Hansen & Li, 2011), resulting in confounding complexities regarding the operationalization of this definition.

For these reasons, maltreatment and early life stress in this paper will be approached from the unifying definition of an experience outside the average expectable environment that has the potential to harm a child. Maltreatment will also be understood

as the absence of the necessary timing, frequency, pattern and nature of experience, as well as the patterns of neural activation caused by these experiences, required to express the genetic potential of a core capability (Perry, 2009).

There has typically been a preponderance of attention given to abuse over neglect despite the fact that both abuse and neglect are mentioned in the literature as having detrimental effects on children. Both abuse and neglect are indentified as commonly studied early childhood stressors and included in the definition under Federal legislation. In 2012, the National Child Abuse and Neglect Data System (NCANDS) reported that there nearly three-quarters (78.3%) of victims were neglected compared to 18.3% who were abused (NCANDS, 2012). Moreover, there is clear evidence that neglect and attachment difficulties in early development may be even more damaging than abuse (Corbin, 2007).

Supporting this notion is the fact that the central deficit in RAD is the child's inability to develop healthy attachment to a caregiver, and the etiology is presumed to be a result of grossly pathological care. The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, classifies "Pathogenic care", as evidenced by at least one of the following: persistent disregard of the child's basic emotional needs for comfort, stimulation and affection; persistent disregard of the child's basic physical needs; and/or repeated changes of the primary caregiver that prevent formulation of stable attachments, all of which and pervasive neglectful and unpredictable care giving behaviors (APA, 2000).

Of significant relevance is the fact that trauma and child maltreatment are not synonymous. While a child may perceive abuse and/or neglect as a traumatic experience, it is because of the predictability and chronicity of the nature of maltreatment/stress. In children who experience pervasive stress, they present with much more complex reactions than children with PTSD, including the lack of discrete conditioned behavioral and emotional responses compared to those with post traumatic stress disorder (PTSD) (Glaser, 2000). The common factor in early life stress, maltreatment and attachment that adversely affects early brain development appears to be those events and conditions in which the child experiences or repeatedly experiences, in a prolonged and uncontrolled manner, circumstances that they perceive as being likely to be significantly life threatening for themselves (Delima & Vimpani, 2011).

Orphan Studies and Reactive Attachment Disorder

Behavioral traits of RAD have been receiving attention since the 1940's secondary to early studies of institutionalized children, and had been first recognized as a clinical disorder in the Diagnostic and Statistical Manual of Mental Disorders III in the 1980's (Hornor, 2008). While recent evidence from severely deprived institutional samples has informed RAD criteria in the DSM-IV-TR & DSM-V, this data is not necessarily generalizeable to expectable child environments in the developed world (Kay & Green, 2013).

While orphan studies have informed us in regard to attachment related problems in the face of early deprivation, not all orphan studies are aimed specifically to assess the characteristics and variability of attachment problems; rather, many aimed to clarify the

impact of institutional deprivation on children (Zilberstein, 2006). Beyond early childhood, RAD in non-institutionalized samples has hardly been studied and there is currently no longitudinal research tracking the developmental progression of the disorder through later childhood and adolescence (Zeanah & Gleason, 2010).

The fact that attachment disorders do not only emerge because of institutional deprivation, and because institutional samples are not generalizable to the population of maltreated children being targeted in this paper, orphan studies will not be reviewed or addressed in this paper. Children who live in families who have been neglected or abused in some way, or those who have experienced numerous foster care placements, or those who were adopted late, can also evidence attachment disorders (Zilberstein, 2006), and this is the population to which this paper is referring.

RAD Diagnosis

RAD has its theoretical underpinnings grounded in attachment theory (Sadock & Sadock, 2007). A diagnosis of RAD is based on the presumption that the etiology is directly linked to pathogenic care, which is evidenced by at least one of the following: persistent disregard of the child's basic emotional needs for comfort, stimulation and affection; persistent disregard of the child's basic physical needs; or repeated changes of primary caregiver that prevent formation of stable attachments (APA, 2000). The other defining factor of RAD is that there is markedly disturbed and developmentally inappropriate social relatedness in most contexts before the age of 5 years (APA, 2000).

There are two types of presentations; the inhibited type and the disinhibited type. In the inhibited type, the child persistently fails to initiate and respond to most social

interactions in a developmentally appropriate way and shows a pattern of excessively inhibited, hypervigilant, or highly ambivalent responses (APA, 2000). In the disinhibited type, there is a pattern of diffuse attachments and the child also exhibits indiscriminate sociability or a lack of selectivity in the choice of attachment figures (APA, 2000). Though there are two distinct subtypes of RAD, recent evidence suggests that a mixed presentation is not uncommon (Hornor, 2008).

Prevalence, Course and Assessment of RAD

According to recent literature, there are limited to no prevalence estimates for RAD, it is one of the least researched disorders in the DSM-IV-TR (APA, 2000; Lake, 2005; Chaffin, et al., 2006). While little is known about the course of the disorder, early childhood maltreatment predicts negative affective, somatic and behavioral outcomes both in childhood and adulthood in a linear fashion (Johnson-Reid, Kohl & Drake, 2012).

Though recent longitudinal data on children raised in institutions is available and informative, there is only one case study in the peer-reviewed literature that has followed maltreated children who were raised in a family and diagnosed in early childhood with RAD. This case study involves RAD in one set of maltreated fraternal twins from 18 months to 8 years (Heller, et al. 2006). Each twin exhibited different patterns of behavior across time; one twin showed extreme inhibition as an infant, controlling behavior as a preschooler, and conduct symptoms with affective disengagement, while the other twin was socially indiscriminate as an infant, self-endangering as a preschooler, and had impulsivity and attention difficulties at 8 years of age.

Questions remain about the nosology of the syndrome beyond age 5 years (Minnis, et al. 2007), and there are currently no validated instruments for assessing or diagnosing RAD (Hardy, 2007; Chaffin, et. al 2006). Adding to the complexity of diagnosis of RAD, is that the tradition of making a psychiatric diagnosis has relied on the interpretation of patient reported symptoms, and experiences and observable signs; a practice that has been criticized for being either invalid or unreliable, or otherwise highly susceptible to personal heuristics (Cheung, 2010).

Lastly, the neurodevelopmental and neurobiological aspects of this disorder are not mentioned in the DSM-IV-TR as defining clinical features, despite the fact that it has been well documented that infants and young children who have been exposed to grossly pathogenic care have a host of neurobiologically induced changes (Tyrka, Price, Marsit, Walkters & Carpenter, 2012; McGowan, et al. 2009; Perry, Pollard, Blakley, Baker & Vigilante, 1995).

Differential Diagnosis and Comorbidity

According to the DSM-IV-TR (APA, 2000), differential diagnosis is essential with RAD as it can be easily mistaken for Autistic Disorder or other Pervasive Developmental Disorders (PDD), Mental Retardation, Social Phobia, Attention Defecit Disorder (ADD), Attention Defecit Hyperactivity Disorder (ADHD), Conduct Disorder and/or Oppositional Defiant Disorder (ODD). Currently, there are no studies examining diagnostic accuracy among the increasing numbers of children who are maltreated being described by clinicians as having RAD (Chaffin, et al., 2006).

A variety of behaviors have been documented to be associated with RAD between the ages of 5 through the teen years, including temper tantrums, mood swings, self-injurious behaviors, attention difficulties (Lake, 2005) and hostility, (Boekamp, 2008). Children with RAD have also been reported to exhibit behaviors such as food hoarding, sneaking or gorging food (Lake, 2005).

As a result, RAD symptoms appear to, or can, overlap with other diagnosis features such as with Conduct Disorder, ODD, and ADHD (AACAP, 2005) and can lead to a failure to diagnose RAD correctly when it is present, and to over diagnose RAD when it is not present (Chaffin, et al. 2006). While some of these symptom overlaps have been associated with RAD, research does not support the conclusion that these behaviors result directly from attachment difficulties, although some of them occur in children who have experienced trauma in association with poor attachment (Zilberstein, 2013).

Auditory and visual attention deficits have been observed in children who have been subjected to neglect and physical abuse, sexual and physical abuse and unspecified maltreatment. However, these studies did not report or control for co-morbidities, or control for co-morbidities in the maltreated group (Hart & Rubia, 2012). Similarly, there have been studies that have found that children and adolescents with poor emotional regulation are more likely to have these types of externalization of behaviors (Cone, Golden & Hall, 2009), and deficits of inhibitory control have been consistently observed in adults with a history of maltreatment, and in adolescents with early life stress. These studies also did not report or control for co-morbidities, or reported but did not control for co-morbidities (Hart & Rubia, 2012). Though children with RAD tend to display a high

number of ADD/HD symptoms, it is not yet clear whether ADHD-like symptoms in children exposed to pathogenic care represent true comorbidity of ADHD or similarities in behavioral dysfunction with a different neurodevelopmental pathway in terms of a phenocopy (Dahmen, Putz, Herpertz-Dahlmann & Konrad, 2012).

To add to the complexities, there is no evidence about whether the aggression associated with RAD is distinguishable from that associated with ODD or Conduct Disorder (Boris & Zeanah, 2005). It is important to noted that maltreated children have been reported to be more likely to perceive threat in even neutral or friendly situations, resulting in over reactivity and aggression (Hanson, 2000). This behavior may be consistent with their experiences, but out of context with the situation. Literature of young maltreated children has established that maltreated children have been shown to interpret and process anger differently than normal children and show sensitivity to angry faces in comparison to normal controls (Weinberg, 2010), supporting the notion that children with RAD can exhibit behavioral manifestations that appear to overlap with other behavioral disorders. On the other hand, none of these studies reported or screened for co-morbidities (Hart & Rubia, 2012).

Being able to differentially diagnose RAD from PDD is also difficult. Early stressful care giving experiences have shown to be causally related to deficits in social functioning (DeBrito et al. 2013). There is evidence that maltreated children demonstrate deficits in their ability to pose emotion expressions, and are also more inhibited in their emotion expression during conflict situations completed to non-maltreated peers (Southam-Gerow & Kendall, 2002). However, the kinds of social problems of children

with attachment problems have been unable to be characterized in detail, and the kinds of social-cognitive problems that underlie these disturbances is not clear (O'Connor & Zeanah, 2003).

The associated V-code diagnoses of Child Abuse, Child Neglect, or Parent-Child Relational problem may appear concurrently with RAD or may be diagnosed instead of RAD when grossly pathogenic care does not result in marked disturbance in social relatedness (Corbin, 2007).

The intricacies of diagnosing RAD are vast, and it is imperative to not under or over diagnose, as misdiagnosing may not only lead to poor treatment decisions, but they can also label and injure the child in other ways. With regard to diagnosing RAD, there is a general consensus that disorders of attachment describe symptom clusters that are unaccounted for by other disorders (Zenah, et al. 2004), such as having experienced grossly pathogenic care.

There are few direct data available about disorders that may be comorbid with RAD (Boris & Zeanah, 2005) and the DSM-IV-TR does not indicate any diagnoses that may be comorbid with RAD (APA, 2000). Other questions include the degree to which these syndromes represent distinct disorders that impair functioning, how they relate to the developmental construct of selective attachment relationships, and the validity of the diagnostic criteria (Gleason, et al. 2011).

Traditional Attachment Theory

To understand RAD is to recognize the importance of the attachment cycle between infants and caregivers.

Attachment theory originated from the work of John Bowlby, who speculated that infants are biologically predisposed to form attachments to available adult caregivers (Dykas & Cassidy, 2011) and that attachment to a primary caregiver is, "rooted firmly in biological theory and requires no dynamic which is not plainly explicable in terms of the survival of the species" (Bowlby, 1958). Attachment theory also suggests that the child's early relationship with the primary caregiver would be the most important predictor of the child's future personality development (Hardy, 2007) and the development of synchronized interactions between the caregiver and infant/child is fundamental to healthy affective development (Schore, 2001b).

Attachment theory posits that humans are a highly social species and human neurobiology is fashioned primarily towards the formation and maintenance of relationships (Bowlby, 1958). Fish, reptiles and amphibians endure largely independent of parenting by producing excess offspring. Among birds, and especially among mammals, smaller numbers of offspring are nurtured to greater or lesser extent, for varying periods of time. There is some parallel between the duration of that nurturance and the social complexity of the species (Dignam, Parry & Berk, 2010).

Attachment and Synchronicity with Caregivers

Infants attend to and react to their caregiver's tone of voice, movement, and facial expressions, and are examples of emotional communication with the caregiver that are

believed to be the very beginning of establishing a secure attachment bond (Hardy, 2007). Numerous studies have shown that newborns (in the first hours of life in some studies) preferentially look towards simple face-like patterns, and gaze into their caregiver's eyes while being fed. Although the exact visual cues that elicit this preference remain unclear, one purpose of this early tendency to fixate on faces is hypothesized to establish bonding with adult caregivers (Johnson, 2001).

Findings from studies on the influence of the amygdala and orbitofrontal cortex suggest that key components of the emotion-processing network and emotion attention interactions begin to emerge early in post- natal life, at the time that infant's visual discrimination abilities undergo substantial experience-driven refinement (Leppanen & Nelson, 2009). The experience of the non-verbal emotions of another through the observation of facial expressions, hearing vocal intonations, or watching body language is instinctive, and infant research indicates that a caregiver and infant can detect and react to affective and physical changes in the other in as little as a fraction of a second (Divinio & Moore, 2010).

By 7-9 months of age, a young child begins to direct attachment behaviors selectively toward a parent figure in times of distress. During this time is also when the infant internalizes socio-emotional leaning, resulting in emotional security (Schore, 2001a). As extensive research on early individual differences in attachment security attests, infants intuitively sort out who is emotionally dependable and how, by 12 months of age, if not much earlier (Allen, 2012). As children age and require less proximity, they continue to turn to their attachment figure when in distress or when facing challenges

(Zilberstein, 2013); in this sense, the attachment system regulates both exploratory and proximity needs. Access to a secure base is developmentally significant because one of the infant's core developmental tasks involves mastering the environment (Dykas & Cassidy, 2011).

Attachment theory postulates that through these experiences, children develop internal representations (internal working models) of the care and protection they received. An internal working model is representative of the internal process the child experiences as a result of the external attachment experiences. Essentially, it is the child's view of how the physical world may be expected to behave, how the caregiver and other significant people may be expected to behave, how the child may expect themselves to behave, and how each interacts with the other (Schore, 2001b). Dependent upon whether the caregiver was consistently affectionate, stable and protective, determines the outcome of the child's attachment pattern; each pattern has been linked to certain caregiver behaviors and child responses (Zilberstein, 2013).

Strange Situation

Mary Ainsworth, who expanded on the works of John Bowlby's attachment theory and internal working models, studied attachment patterns in a social experiment called the "Strange Situation". Ainsworth postulated that infant-mother attachment could be conceived as related to separation anxiety, fear of the strange and strangers, and exploration (Ainsworth & Bell, 1970). These attachment behaviors have been studied in the laboratory by placing caregivers and infants (12-18 months of age) in situations to observe how exploratory behavior was affected by mother present, mother absent or other

conditions, and has been repeated in numerous settings across the world (Svanberg, 1998).

The child's attachment status is assumed to be based on the child's previous attachment experiences and reflect the child's internal working models, and have been hypothesized in traditional attachment theory to be reasonably stable over time (Glaser, 2000). Attachment style is measured in infancy and early childhood by the Strange Situation Test, which yields one of four types of attachment styles: secure (B), ambivalent/resistant (C), anxious/avoidant (A), and disorganized/disoriented type (D). These four main patterns of infant-parent attachment are unlikely to be determined by a single property of the child such as temperament (Steele, 2004).

In normal development, children show distress upon separation from an attachment figure; however are quickly comforted upon reunion, demonstrating secure attachment (Connors, 2011). Caregivers of secure children show responsiveness and sensitivity to the child through verbal and non-verbal behavior (Zilberstein, 2013) and provide a secure base for the child by allowing a healthy amount of both exploration and security (Cornell, 2008). A secure base indicates that the child trusts the parent enough to be protected from dangers and finds comfort in the caregiver's presence.

The processes of attachment occur cross-culturally (Gleason, et al. 2011), and attachment theory has a high convergent validity; phenomena studied in numerous countries by researchers of different disciplines applying various methods to different age groups find many points of agreement (Connors, 2011).

Attachment Styles

The disorganized/disoriented attachment style is found predominately in infants and children who have been abused or neglected (Schore, 2001b; Cornell, 2008; Zilberstein, 2013; Schore, 2001a; Hardy, 2007; Marvin & Whelan, 2003; Baer & Martinez, 2006), and is the attachment pattern associated with RAD (Schore, 2001b; Hardy, 2007; Cornell, 2008). This type of attachment style has also been found to be a result of the absence of parental loss or trauma, caregiver mood disorder or substance abuse, poverty, institutional care, maltreatment or witnessing domestic abuse (Hardy, 2007), all of which have enduring effects on the physiological response system.

It has been proposed that for these infants and children, the caregiver is both the source of security and the source of danger (Van Der Host, LeRoy & Van Der Veer, 2008), and represents the absence of an organized strategy to deal with stress (Baer & Martinez, 2006). Behaviorally, these children present with contradictory approach/avoidance behavior associated with frightening or frightened behavior by the caregiver (Creeden, 2004), and fluctuate between craving and fearing closeness with the caregiver, which could be exhibited through freezing, stilling and apprehension, intermingled with advances toward the attachment figures (Zilberstein, 2013). Empirical evidence has corroborated that disorganization is more robustly predictive of later maladaptation than is organized insecurity, both within the attachment system and within the realm of psychopathology (Weinfield, Whaley & Egeland, 2004).

Both the anxious/avoidant attachment style (A) and ambivalent/resistant (C) have also been found more commonly among maltreated children (Glaser, 2000). Children

classified as the anxious/avoidant type present with behaviors that resemble rejection and tend to ignore the caregiver's departure and return, and actively avoid the caregiver's attempts to regain contact (Hardy, 2007). These children do not explore freely, nor do they seem to enjoy contact with their caregiver. They ignore or avoid their caregiver after separation and show little preference to their caregiver over a stranger. These children also exhibit more anger and aggression toward their parent and appear to feel conflicted between approach and avoidance (Baer & Martinez, 2006). Caregivers of the avoidant type typically reject their children's signals, avoid physical contact and withdraw from them when the children show distress (Connors, 2011).

Children and infants who are classified as ambivalent/resistant types present with great distress upon separation from their caregiver, and alternate between displays of anger and intense proximity seeking when reunited (Baer & Martinez, 2006). Caregivers of these children are typically unpredictable, inconsistent and insensitive, though they do show warmth at times (Cornell, 2008).

It is noted that the RAD diagnosis does not fit neatly into the categorization of the four attachment styles that have been listed by Ainsworth, and researchers do not agree upon a clear understanding of how Ainsworth's attachment categories relate to the clinical diagnosis of RAD (Cornell, 2008).

A Touch of Ethology

Both Bowlby and Ainsworth viewed attachment from an evolutionary perspective, noting that attachment behaviors and classifications were indicative of the biologic function of the infant-caregiver attachment relationship, and suggested that

attachment was being built into the nervous system, in the course of and as a result of the infant's experience of transactions of the caregiver (Schore, 2001b). In an effort to bridge the gap between their hypotheses and science, Bowlby turned to ethology, which is a discipline that observes and studies animals in their natural habitat in order to understand how their instinctive behavior contributes to adaptation and actual survival (Sable, 2004).

Bowlby was significantly influenced by Konrad Lorenz, an ethologist, who had termed the phenomenon of imprinting after observing many bird species formed a social preference for the first moving, conspicuous object they encountered after hatching. From studies on imprinting, Bowlby assumed that processes analogous to imprinting likely also occurred in mammals, including goats, sheep, monkeys and possibly humans (Lickliter, 2008), and postulated that these instinctive behaviors were also present in infants and young children, in their requirement to maintain close contact and proximity with their caregivers through attachment. Additional related attachment behaviors have also been noted in studies of other ground-living nonhuman primates, studies of these species in captive colonies, and in laboratories (Ainsworth & Bell, 1970).

Significantly adding to the studies of non-human primate attachment were experiments conducted by psychologist, Harry Harlow. In experiments with young rhesus monkeys, he removed them from their mother's at birth, and provided them with the choice of two varieties of dummy models in which to cling and from which to take food- one with cloth and no food and another with no cloth and food. Results strongly suggested that the preferred model was the one which most comfortable to cling, rather than the one which provided the food (Van Der Horst, LeRoy & Van Der Veer, 2008).

There are research studies of both humans and animals that have found that separation from of loss of an attachment figure could, by itself, cause fear and anxiety, affecting both attachment and exploratory behaviors (Sable, 2004).

In fact, in Harlow's experiment with the rhesus monkeys, the monkeys who had cloth mother surrogates were terrified when placed in a strange environment, and did not explore their surroundings if their cloth dummy mothers were absent. If the cloth dummy mother was present, the infant monkeys would cling to it and then explore (Sadock & Sadock, 2007).

This ethological framework of attachment was the very beginning of bridging the gap between the biological and the psychological aspect of attachment, and began suggesting that attachment was to no longer be viewed as simply a strategy for meeting basic needs, but as an instinctual, and biologically innate mechanism, by which both Bowlby and Ainsworth endorsed. In the half-century since the work of Bowlby and Harlow, the notion of instinctive behavior gave way to an appreciation that behavioral development is much more than the unfolding of an innate program, independent of the experience and context of the organism (Lickliter, 2008).

Neuropsychobiology of a Modernized Attachment Theory

Attachment theory postulates that the complexities of normal development are unattainable by simply looking through only the lens of environmental factors, and that it requires an integration of neuroscience and psychology to be able to adequately do so (Schore, 2001a).

While traditional attachment theory relies on theory that the quality of early relationships between caregivers, infants and young children, recent literature from developmental neuropsychology has recently been able to highlight the detrimental effects of early life stress on the developing brains by means of the stress response systems during periods of inadequate attachment security. Similarly, the symptoms of RAD can be viewed as cluster of behavioral symptoms expressed by the child as a result of environmentally induced neurobiological changes.

The fact that many attachment disorders begin in infancy reflects how the human brain is organized and that the most brain development takes place during the first early years of life (Lake, 2005). An overview of the anatomy, mechanisms and milestones of brain development will be discussed, and the main cortical and subcortical regions associated with early childhood maltreatment and early life stress will be emphasized.

The Developing Brain

The brain develops in a sequential and hierarchal fashion, from least complex (brainstem and cerebellum) to the most complex (limbic and cortical areas) in a back to front direction (parietal lobe to the frontal lobe) and become fully functional at different times during early childhood (Perry, et al. 1995).

The two components of the brain that are the least complex, and therefore begin developing first in utero, are the brainstem and the cerebellum. The brainstem is the lower extension of the brain, and is connected to the spinal cord and consists of the midbrain, pons and medulla oblongata. The brainstem passes messages back and forth between various parts of the body and the cerebral cortex. The primitive functions that

are essential for survival are located here, such as breathing, regulation of blood pressure, heart rhythms, swallowing and sleeping patterns. The cerebellum is located at the back of the brain and is responsible for motor activity and maintains balance and movement (Carlson, 2010), and grows most rapidly during the first year of life (Papalia, Olds & Feldman, 1999). These areas of the brain must be intact for the infant to survive, and any malfunction is immediately observable.

The brain is divided into two hemispheres, each of which is divided into four lobes and develop from least complex to most complex in terms of higher emotional and cognitive functioning, in the following order: the parietal lobe, occipital lobe, temporal lobe and frontal lobe. The lobes are covered by the cerebral cortex, which is a flat sheet of cells about 2.5cm thick, lying just beneath the cerebrum, covering the outer surface of the brain, forming the corrugated surface of the four lobes of the cerebral hemisphere (Rick & Douglas, 2007).

The parietal lobe is the first of the lobes to develop, and plays an integral role with integration of sensations, spatial awareness and perception. The parietal lobe consists of three cortical regions, including the postcentral gyrus (processes tactile and proprioceptive information), somatosensory association cortex (integrates and interprets sensations relative to body position and orientation in space), and the primary gustatory cortex (involved with the interpretation of the sensation of taste) (Blumenfeld, 2010).

The occipital lobe is the second lobe to develop and plays an integral part in the processing, integration and interpretation of visual stimuli. The occipital lobe consists of two cortical regions, the primary visual cortex (responsible for sight, recognition of size,

color, light, motion and dimensions), and the visual association area (interprets information acquired through the primary visual cortex) (Blumenfeld, 2010).

The temporal lobe is the third lobe to develop and plays an integral role in the functioning of hearing, organization and comprehension of language and information retrieval such as memory and memory formation. The temporal lobe consists of three cortical regions, the primary auditory cortex (responsible for hearing), the primary olfactory cortex (interprets the sense of smell), and Wernicke's area (involved with language comprehension) (Blumenfeld, 2010).

The frontal lobe is the fourth lobe to develop and is the largest region of the brain, comprising of nearly one-third of the cerebral cortex. This lobe plays an integral role in memory formation, emotions, decision-making and reasoning and personality and consists of four cortical regions, including the precentral gyrus (controls movements of the body), Brocas area (controls speech and language comprehension), orbitofrontal cortex (involved in arousal and calming) and the olfactory bulb (responsible for sensation of smell) (Blumenfeld, 2010).

Microneurodevelopmental Processes

Around 15 weeks of age, the cerebral hemispheres begin growing, and expand towards each other over the top of the head and extend towards the rear of the skull, so that the thalamus becomes centrally buried deep beneath them. The surface of the cerebral hemisphere then begins to fold in on itself around 24 weeks of age, at which time it triples in thickness as new connections are being formed between neurons

(Balbernie, 2001), specifically by the differentiation and growth process by the branching of dendrites in neurons.

During the initial generation of the nervous system in utero, neural progenitor cells are located in the ventricular zone of the developing central nervous system (CNS), where the number of progenitors increases via mitosis. Upon leaving the ventricular zone, these cells cease to divide, and enter into the mantle where they mature and differentiate into neurons (Cheung & Ip, 2008). Once formed, neurons typically migrate to the correct position in the cortex by moving along the long fibers of cells called radial glia, which act like ropes extending from the inner to outer surfaces of the brain. Migration occurs between 3 months gestation and during infancy. Once neurons find their way to the appropriate location, they begin to differentiate and become more specialized over time (Spencer-Smith & Anderson, 2009); differentiation occurs between 6 months gestation and throughout infancy.

Simultaneous to differentiation is the process of extending axons and dendrites. As cells develop receptor mechanisms at their neuronal bodies, spontaneous electrical activity may signal the initial development of dendrites and incoming axon processes induce dendrites to form (Webb, Monk & Nelson, 2001). Dendrites consist of spines, which are modifiable and are the targets of most synaptic inputs to a neuron, and the branches, or sprouts, grow off of the neuron in order to establish new synaptic contacts. While there is a general agreement that dendritic growth in neocortical neurons occurs between the third trimester and 24 months of age, there has been disagreement as to whether dendritic growth continues at a slow rate after 24 months, whether the size of

dendritic trees are stable after 24 months, or whether there is pruning of dendrites (Huttenlocher, 1999). Based on current research, it is believed that experience can continuously organize neuronal activity and have short and long term effects on spine remodeling, including formation, elimination, size and shape changing and axonal sprouting (Berlucchi, 2011).

Many cortical neurons also become myelinated by myelin, which is a fatty sheath that surrounds neurons and helps them transmit signals more quickly. White matter in the brain consists of myelinated neurons full of synaptic activity, while grey matter consists of unmyelinated neurons. Myelinated axons send signals at velocities that are about 50-100 times faster than unmyelinated axons (Belsky & De Haan, 2010). The process of myelination begins to form in-utero, rapidly develops between 7 and 15 months of age (Schore, 2000). Longitudinal structural imaging studies show a linear increase with age in white matter that is most pronounced between early childhood and adolescence, but undergoes progressive increase until peaking at around age 45. Gray matter undergoes substantial non-linear changes with an increase up to age 10, thought to be due to glial cell proliferation, dendritic and axonal branching and a decrease after age 10 due to synaptic pruning and myelination (Hart & Rubia, 2012).

Cortical thickness occurs exponentially by the massive connections made by neurons. At birth, the human brain weighs approximately 400gm, and then rapidly increases to 1,000gm by 12 months of age. This growth spurt continues into 24 months of age (Glaser, 2000), at which time the maximum density of synapses is also reached (Belsky & De Haan, 2010).

Synaptogenesis

The process of synaptogenesis, when functional synapses form between neurons, begins in the embryo and extends into early postnatal life (Waites, Craig & Garner, 2005); however, it is unclear how extensively and for which brain areas this occurs and at which periods of growth (Thompson & Nelson, 2001).

Neurons transmit information to other neurons at their synaptic contacts, and at a chemical synapse, an electrical signal from the pre-synaptic cell is converted into a chemical signal that can be transferred through extracellular space to the postsynaptic cell. In synaptic transmission, an electrical signal is transferred from the soma in the cell body down the axon and signals the release of chemical messengers into extracellular space (Webb, et al. 2001). This process allows for intercellular communication, with most synapses occurring between axons and dendrites. This process is very complex, and necessitates that differentiation and migration appropriately occurs in order for the synapse to form and become fully functional. Furthermore, synaptic activity determines whether these synapses will be stabilized or eliminated (Waites, et al. 2005), and since synaptogenesis occurs in different areas of the brain at different times, this process is more sensitive to disruptive experiences at specific points during development (Perry, 2009).

Pruning

Subsequent to the peak level of synaptic density being reached around 24 months of age, the elimination process begins. Synapses are being constantly removed, yielding a marked decrease in synaptic density (Chechik, Meilijson & Ruppin, 1998), which occurs

throughout widespread brain regions, and follows a dorsal to frontal order, up until around 5 years of age where they then remain stable throughout the rest of adulthood. Pruning is imperative for normal development (Spencer-Smith & Anderson, 2009), and includes the loss of synapses, and refers to environmentally regulated changes in the density of synapse per unit of dendritic length, not the loss of the entire neuron (Webb, et al. 2001).

When a neural pathway is activated, all the synapses that have become engaged will store a chemical pattern and this is strengthened by repeated use. When this signal transmission reaches a certain threshold level, the synapses involved become exempt from future elimination (Balbernie, 2001). It is hypothesized that these stabilized synapses will survive while those that were not frequently used during childhood will be eliminated. The experience dependent process of pruning appears to be regulated by competitive interactions between neuronal connections, such that those neurons that remain inactive or are rarely activated are eliminated, and those that are actively stimulated by experience are strengthened and maintained (Belsky & De Haan, 2011; Webb, et al. 2001). While some researchers have treated this phenomenon as lacking any significance, it appears that synaptic elimination has shown to be correlated with experience-dependent activity and neuronal plasticity (Chechik, et al. 1998; Fox & Rutter, 2010) and that the overproduction of neurons is potentially an adaptive function for the brain by creating an overflow that is available to repair injury (Johnston, 2009).

Right and Left Hemispheres

The right hemisphere is the dominant side of the brain up until approximately 36 months of age, and grows more rapidly, and is more active, than the left hemisphere during this time period (Siegel, 2001; Schore, 2001a). The areas of the right hemisphere have extensive reciprocal neural connections with the autonomic nervous system, regulate physical reactions to affective stimuli (Hardy, 2007), and also have extensive reciprocal connections with the limbic system (Schore, 2000).

The areas of the right hemisphere within the prefrontal cortex that regulate bodily function and emotion appear to be predominant during this timeframe (Schore, 2002), enabling the development of patterns of communication prior to developing left-hemisphere verbal based skills (Divino & Moore, 2010). Preferential hemispheric development is significant because the post-natally maturing orbital prefrontal areas in the early developing right brain are centrally involved in attachment, emotion, stress regulation, and the control of social behavior (Bradshaw & Schore, 2007).

The left hemisphere mediates most linguistic behaviors, beginning within the third year of life (Divino & Moore, 2010), and takes a back seat during the first 2-3 years of life while the regulation of affective stimuli takes priority.

Corpus Callosum

The two cerebral hemispheres of the brain are connected through the corpus callosum, which is an axonal bridge responsible for communication between the right and

left hemispheres (Rick & Douglas, 2007). Inter-hemispheric communication includes that of emotion, and higher cognitive abilities (Hart & Rubia, 2012).

This structure is the most prominent white mater structure in the brain, contains about 200 million mylenated fibers, and increases in volume throughout childhood into young adulthood (Belsky & De Haan, 2011). White matter is white due to the myelin sheath coating, and is comprised of axons and connects different locations of gray matter to each other, whereas gray matter is absent of myelin sheath and is comprised of cell bodies. The anterior section of the corpus callosum develops between 3 and 6 years of age, assisting in vigilance and planning of new actions, and the posterior corpus callosum develops between 6 and 13 years of age, assisting in language and associative memory (Pechtel & Pizzagalli, 2011).

Limbic System

Included in the limbic system are a variety of structures extending from the forebrain to the brainstem; however, the most applicable structures of the limbic system related to early childhood maltreatment are the cortical areas of the amygdala, hippocampus and hypothalamus, which are located in the temporal lobe, and on the divide between the cerebral cortex and the brain stem.

The limbic system communicates to other higher and lower brain areas when something emotionally significant occurs (Balbernie, 2001) and controls the emotional interpretation of incoming stimuli and recalled memories (Davis, 2006), as well as autonomic and neuroendocrine control (Blumenfeld, 2010). The limbic system develops rapidly between 7 and 15 months of age (Schore, 2000), and around 9 months of age is

when the limbic and cortical association areas have matured sufficiently, whereby enabling distal modes of communication and engaging in joint attention (Balbernie, 2001).

The hippocampus is located on the inside fold of the temporal lobe, projecting to the amygdala and prefrontal cortex (Petchel & Pizzagalli, 2011), and is important in memory, learning, and the interaction between perception and memory (Davis, 2006). Because the hippocampus is not yet matured within the first 12 months of life, during those months the infant only has available implicit forms of memory, which includes emotional, behavioral, perceptual and somatosensory memory (Siegel, 2001). When implicit memories are activated, the individual at any age will be unable to experience an internal sensation that something is being recalled; however, the implicit memories will influence our emotions, behaviors, or perceptions directly, without awareness of their connection to some experience from the past.

Once the maturation of the hippocampus begins shortly after 1 year of age, explicit encoding is available, which includes semantic (factual) and autobiographical (episodic) types of memory (Siegel, 2001). For both types of explicit memory, the individual is able to recall the memory as well as the associated internal sensation, along with a sense of self at that time in the past.

The amygdala is located in the anterior portion of the medial temporal lobe and plays a crucial role in guiding behavior based on emotional/threat related stimuli (Mehta, et al. 2009), and plays a role in fear conditioning and the control of aggressive, oral, and sexual behaviors (Rick & Douglas, 2007). Simulation of the amygdala produces

autonomic reactions associated with the fight or flight response, including increased heart rate and blood pressure, freezing behavior in animals, feelings of fear and anxiety in humans, and increased plasma stress hormone levels (Thomas, et al. 2014).

The amygdala also assigns emotions to memory (Davis, 2006), as the hippocampus is connected reciprocally to the amygdala and plays a crucial role in the acquisition of fear responses and in memory consolidation of emotional experiences and stimuli (Van Der Werff, et al. 2012). Enhanced memory for stressful or emotionally arousing events is a well-recognized, highly adaptive phenomenon that helps us to remember important information (Roozendaal, McEwen & Chattarji, 2009).

Data regarding the development of the connections of the amygdala come primarily from monkeys and suggests that most of the connections are already established by the time of birth or soon afterwards. Myelination in the human amygdala begins in the first months of life, with some aspects appearing to mature by 10 months of age (Belsky & De Haan, 2010).

Hypothalamus

The hypothalamus is located in the center of the brain, in the temporal lobe, and is a regulatory structure that controls the pituitary gland and converts neural activity into hormonal signals (Balbernie, 2001). The hypothalamus is developed in utero (Koutcherov, Mai, Ashwell & Paxinos, 2002) and contains both neurons and neuroendocrine cells whose activity can be measured in the plasma levels of hormones secreted by those cells. Those hormones contain various hypothalamic nuclei which have specific cell functions: the suprachiasmatic nucleus is the hypothalamic clock; the

vasopressin neurons of the supraoptic and paraventricular nuclei are involved in antidiuresis; and the cortocotropin-releasing hormone neurons of the paraventricular nucleus are pivotal in stress response (Swaab, 1995).

Prefrontal Cortex

The prefrontal cortex is located in the prefrontal cortex region of the frontal lobe and is connected to the limbic system (Davis, 2006). This region of the brain is the seat of executive functions (inhibitory control, working memory, focus and attention, problem solving, reasoning, planning and future oriented thinking), and is reciprocally interconnected with limbic and brainstem structures associated with the stress response and emotional arousal (Blair & Raver, 2012). Network connections between the prefrontal cortex and the amygdala are involved in the management of stress, emotion and impulses (Carrion, Wong & Kletter, 2013). It also monitors the state of the body and evaluates the meaning and value of sensations and is the operational control center for sorting and managing feelings (Balbernie, 2001). The prefrontal cortex begins a major maturational change at 10-12 months of age (Schore, 2000) and matures relatively later in life.

Vagus Nerve

The vagus nerve, also known as cranial nerve X (CN X), is a parasympathetic efferent nerve that relays information to many areas of the brain (Sadock & Sadock, 2007), and originates from four nuclei in the medulla oblongata; the dorsal nucleus, nucleus ambiguous, nucleus of tractus solitarius, and spinal nucleus of trigeminal nerve. Eight to ten rootlets extend from the nuclei forming the fibers of the vagus nerve. The

nerve exits the cranium via the jugular foramen and lies in the carotid sheath at the neck level between the carotid artery and the internal jugular vein (Ogbonnaya & Kaliaperumal, 2013).

The vagus nerve's efferent functions serve as messengers for signals from the brain to the viscera, and this role has been underemphasized in the literature. With the exception of cranial nerve I (CN1) for olfaction, CN X has been the most intriguing, and arguably the most misunderstood (George, et al. 2003).

Since 1985, a tremendous amount of work has been done on how the sensory afferent fibers from the vagal nerve cause brain changes (Sadock & Sadock, 2007). Through these routes, it is hypothesized that the nucleus of tractus solitarius sends direct projections to the amygdala and hypothalamus, through the pons and raphe (the primary serotonin containing areas of the brain) and other projections are made to the locus coeruleus (the primary norepinephrine containing area of the brain), which also connects with various forebrain structures including the obitofrontal cortex and prefrontal cortex (George, et al. 2003).

Developmentally, the number of myelinated vagal fibers increases linearly from 24 to 28 weeks gestation until full-term birth, when the number of fibers is comparable to those observed in adolescence. In full term infants, the myelination process is active during the first year of life, particularly during the first 3 months (Porges, 2007).

Neurochemical and Biological Threat Response

The human mind and body have sets of primitive, deeply ingrained physiological and psychological responses to threat. The role of the stress response system is the sense

distress such as hunger, thirst, cold, or a different type of threat, and then act to address this challenge to homeostasis to promote survival.

For adults, the response to an immediate threat is "Fight or flight", where there are immediate and short-term biological responses, and the adult has the capacity to react physically to the threat. On the other hand, with infants and young children who are faced with an immediate threat, the classic "Fight or flight" response is impractical due to their developmental limitations and therefore, their distress is noted by means of crying and screaming, at which point the caregiver is expected to become that infant or child's external regulator. The primary source of the patterned somatosensory interactions that provide the organizing neural input to the developing stress response system is the primary caregiver (Perry, 2009), and the normal development of the stress response system is thus experience dependent.

When the stress response system is activated through the presence, or the perceived presence, of an immediate threat, the body responds through a large increase in activity of the sympathetic nervous system by means of the autonomic nervous system, resulting in increased heart rate which allows more blood to be pumped, increased blood pressure, dilation of the pupils to enhance visual ability, increased respiration enhancing oxygen intake, release of stored sugar to be utilized as an energy source, an increase in muscle tone, a sense of hypervigilance and tuning out of all noncritical information (Klein, 2000).

This complex set of interactive processes includes activation of the autonomic nervous system, the immune system, the limbic-hypothalamic-pituitary axis (HPA) with a

concurrent peripheral release of andrenocorticotrophic hormone and cortisol, along with other stress response neural systems in the brain (Perry, et al. 1995). Once the sympathetic nervous system is activated by means of the autonomic nervous system, the HPA is simultaneously activated. Serotonin shows rapid elevations in the limbic system following the onset of stress and is also involved in the activation and control of the L-HPA axis (Frigerio, et al. 2009).

The activation of the HPA axis causes the neurotransmitter norepinephrine (NE) to be released by the locus coeruleus, as well as noradrenaline (Feder, Nestler & Charney, 2009) which activates the amygdala, causing the hypothalamus to release corticotrophin hormone (CRH) (Watts-English, Fortson, Gibler, Hooper & DeBellis, 2006; Schore, 2002) as well as arginine vasopressin from the paraventricular nucleus of the hypothalamus (McCrory, DeBrito & Viding, 2010). Vasopressin acts on a wide variety of neurons in the amygdala and the excitatory actions of vasopressin might contribute to the behavioral stress response and is known to modulate emotional memory and anxiety (Joels & Baram, 2009). NE originates from the pons, which is located on the brainstem; CRH is released from the axon terminals in the hypothalamus and acts on receptors in the pituitary; it is also expressed in neurons in the amygdala, hippocampus and the locus coreulus (Joels & Baram, 2009) and influences rapid secretion of adrenocorticotrophic hormone (ACTH) from the corticotrophs of the anterior pituitary (Brunson, Avishai-Eliner, Hatalski & Baram, 2001). ACTH then stimulates the release of cortisol from the adrenal gland, which feeds back through the pituitary, hypothalamus, hippocampus and amygdala. Both the CRH and vasopressin travel to the anterior pituitary where they

stimulate the release of ACTH, which in turn interacts with the receptors of the cortex of the adrenal gland. ACTH travels through the bloodstream and acts on the adrenal glands to release glucocorticoids (Brunson, et al. 2001), which are then released throughout the brain and the body and bind to mineralocorticoid and glucocorticoid receptors (Petchel & Pizzagalli, 2011), primarily in the hippocampus (McCrory, et al. 2010). In addition, glucocorticoids and CRH interact with other neuropeptides, such as oxytocin and neurotransmitter systems, such as dopamine and serotonin, resulting in widespread influences of stress level activation (Gunnar, Fisher & The Early Experience, Stress and Prevention Network, 2006).

The intense flurry of elevated catecholamine and neuropeptides trigger a hyper-metabolic state within the developing brain, which is meant to last for only a short period of time. In circumstances where there are ongoing and chronic threats, the biological threat response will be prolonged.

Through inconsistent nurturing and unpredictable care giving, the patterned repetitive neural stimulation will cause use dependency of this stress system, which results in abnormal triggers and ultimately abnormal development. Early life stress, childhood adversity and familial function are linked to the alteration of basal and stress-induced activity of the HPA, along with an increased risk for multiple forms of psychopathology, as the alteration of the HPA is implicated in the pathogenesis of psychopathology (Tyrka, et al. 2012; McGowan, et al. 2009).

There have been several studies that support the hypothesis that the activity of the HPA in early childhood is socially regulated and that dysregulation may accompany

maltreatment (Twardosz & Lutzker, 2010). Animal studies support that alterations in the HPA system has been associated with early maternal separation in rats, squirrels, monkeys, and macaques, and rat pups who have not been handled during early life (Gilles, 1999).

Stressful experiences do not need to necessarily be extreme to alter this system, but experiences that are cumulative in nature, as well as the timing, duration, and severity of the stress, can have this effect (Bryck & Fisher 2012). Reminders or conditioned stimuli and perceived threats may also cause continuous reactivation of this neurobiological stress system and alter the responsivity of this system (Watts-English, et al. 2006), despite being distanced from the original threat(s). Similarly, research has shown that internal imagery can activate and stimulate the same brain systems as do actual sensory perceptions; thinking or dreaming about an experience activates the same pathways as are active during the experience (Divino & Moore, 2010). Additionally, every day stressors that previously may not have elicited any response may prematurely elicit and exaggerated bio-neurochemical stress responses, which in turn means that the infant or young child will be very transitioned from being mildly anxious or threatened to being terrorized.

Effects on the Brain

The continuous reactivation and sensitivity of this stress system is invisibly daunting on the developing brain and body, and stress experienced from abuse and/or neglect can impact brain development, producing differences in its anatomy and

functioning, resulting in a brain that is different form one that develops in the absence of abuse/neglect (Twardosz & Lutzker, 2010).

Undifferentiated neural systems in the developing brain are critically dependent upon sets of environmental and micro-neurodevelopmental processes to appropriately organize from their undifferentiated immature forms. Lack of, or disruption of, these critical cues, such as by early life stress and maltreatment can result in abnormal neuronal division, migration, differentiation and/or synaptogenesis, and myleination (Perry, et al. 1995), especially in the limbic areas when they are in critical periods of synaptogenesis (Schore, 2002).

Recent studies in healthy participants and community samples have added to the evidence that childhood maltreatment is associated with morphological brain alterations, and pre-clinical studies have previously shown that childhood maltreatment can result in morphological changes in brain structure (Chaney, et al., 2014).

Structural changes in the hippocampus, prefrontal cortex, corpus callosum (Spinelli, et al., 2009) and amygdala (Schore, 2001a) are associated with long term arousal of the neurochemical and biological stress systems, play key roles in memory, anxiety, mood modulation and decision-making (Gunnar & Adam, 2012; McEwen, 2007) and have received particular attention in studies of the neural correlates of childhood maltreatment (Belsky & De Haan, 2011; Teicher, et al., 2009). Abuse or maltreatment in early life has also been shown to cause underdeveloped brain regions to atrophy (Balbernie, 2001), occurs through the process of the overpruning or retracting of dendritic

fields, which reduces the potential sites of synaptic connectivity with distant cortical and subcortical inputs (Schore, 2001a).

Generally speaking, a relationship between adverse childhood experiences and psychiatric disorders has been frequently emphasized in the literature (Pietrek, Elbert, Weierstall, Muller & Rockstroh, 2013).

Hippocampus

Exposure to early abuse and early life stress has been associated with reduced volume or synaptic density of the hippocampus (Teicher, Tomoda & Andersen, 2006). Reductions in hippocampal volume have been consistently found in adults with PTSD, including adults with a childhood history of abuse (Carrion, et al. 2013). Although there are relatively few studies examining children with maltreatment histories, and there is some evidence of hippocampal volume deficits compared with healthy controls (Hart & Rubia, 2012).

Hippocampal reduction is postulated to be due to chronic stimulation of the hippocampal glucocorticoid receptors by circulating glucocorticoids. The glucocorticoids also appear to reduce hippocampal dendritic branching. Generally, elevated glucocorticoids impair neuronal growth and survival, diminish neurotrophins and modify immune function and accelerate cellular aging, all of which have been associated with early life stress (Tyrka, Price, Marsit, Walters & Carpenter, 2012).

Animal studies show that exposure to high levels of stress hormones has toxic effects on the developing hippocampus (Teicher, 2000). Psychological stress in monkeys

and tree shrews result in decreased dendritic branching and/or neuronal loss in the hippocampus (Kitayama, Vaccarino, Kutner, Weiss, & Bremner, 2005).

Prefrontal Cortex

The prefrontal cortex (PFC) is the brain region that is most susceptible to damage in childhood and adolescence due to its protracted development, and is considered an important target for abnormal development in children and adults who have been exposed to severe environmental stressors such as maltreatment.

There have been mixed findings from studies comparing PFC volume of children with maltreatment histories compared to those without maltreatment histories (Hart & Rubia, 2012). However, volume reductions in the prefrontal cortex have been demonstrated in several studies of adults who reported an early history of childhood maltreatment (Edmiston, et al. 2011). In some studies, dendritic branching in the prefrontal cortex was found to be reduced as a result of the abundance of glucocorticoids (Ventura-Junca & Herrera, 2012), as this increase in excitatory catecholamine levels appears to induce changes to both peripheral and central stress circuits (Blair & Raver, 2012).

In healthy individuals, the PFC supports the ability to filter and suppress information and actions in factor of shifting attention to relevant information and responses. Human studies have shown that individuals with prefrontal cortex lesions have deficits in shifting attention, and animal studies have shown that when the prefrontal cortex is damaged, unlearning of a conditioned response does not occur normally, resulting in a marked increase in fear reactivity (Carrion, et al. 2013). Consistent with

these animal studies, the authors Heberlein, Padon, Gillihan, Farah & Fellows (2008) showed that patients with prefrontal cortex damage have difficulty interpreting social and emotional cues.

Amygdala

There is conflicting evidence for structural abnormalities of the amygdala in maltreated children, and the results of studies that have measured amygdala volume in adults with a history of childhood maltreatment are also inconsistent (Hart & Rubia, 2013). Despite the inconsistent evidence with the population of maltreated children and adults, other behavioral and neurobiological evidence suggests that atypical amygdala development is associated with anxiety. In anxious children and adolescents, amygdala volumes are atypically larger relative to typically developing individuals, and amygdala volumes also positively correlate with levels of anxiety in adults (Tottenham, et al. 2009).

In adult animals, psychological stressors or direct administration of stress hormones increases dendritic arborization and formation of new spines. Early life stress has also been found to have long-term effects on rat pups who were separated from their mothers during the neonatal period, and showed greater amygdala response to stress as adults than non-separated rats (Tottenham, et al., 2009).

Corpus Callosum

The most convincing evidence for the effects of stress on brain development pertains to the corpus callosum. High levels of stress hormones can interfere with the myleination of corpus callosum axons during their development by suppressing the division of glial cells that produce myelin, which makes the axons less efficient in

conducting nerve impulses between the two hemispheres of the brain (Twardosz & Lutzker, 2010).

Three separate studies with abused and neglected children by (De Bellis, et al. 2010; Teicher, et al. 2004; Teicher, et al. 1997), have linked maltreatment with reduction in corpus callosum size. Differences in corpus callosum size are present early and possibly persist throughout life (Jackowski, et al. 2011). Additionally, corpus callosum size was reduced in male primates that were isolated (nursery-reared) during early development relative to semi-naturally reared primates (Reicher, Dumont, Ito, et al. 2010).

Experience Guided Neurodevelopment

It is apparent that there are specific developmental trajectories for distinct areas of the brain at different timeframes during early development, and that stress can have significant impacts on the structure and function of the vulnerable developing brain. In the following section, critical periods of development will be discussed, along with the biological underpinnings by which early life stress. Experiences and genetics are confounding and interconnected variables in how the brain systems underlying emotion and behavior are affected and will be briefly discussed.

Critical Periods

There are certain periods during early development when experiences have a more significant effect than others, and are known as sensitive or critical periods. Critical periods refer to time windows where expected experiences are necessary for a particular

brain function to develop normally, and because specific experiences potentiate or inhibit neural connectivity at key developmental stages (Fox, Levitt & Nelson, 2010).

Once a given brain area has passed the stage when it is amenable to refinement, its critical period has ended and subsequent opportunities for re-wiring are significantly limited, but not always altogether impossible (Balbernie, 2001). It is well known that during such periods, experiences may have profound programming and organizing effects (Heim & Binder, 2011; Perry, et al. 1995; Siegel, 2001), and can be a double edged sword, considering that during such times of heightened plasticity the window is not only open to beneficial effects, but also destructive ones.

The timeframe and mechanism by which developing infant's brain is maximally vulnerable to deleterious environmental events is during the period of synapse overproduction followed by what has been hypothesized to be environmentally driven synapse elimination (Schore, 2002; Glaser, 2000; Thompson & Nelson, 2001; Monk & Nelson, 2001) due to the availability of unspecified or labile synapses, including competition for synaptic sites and persistence of normally transient connections (Thomas, 2003). The environmental experience produces patterns of neural activity, targeting those synapses that will be selected for preservation. The neural activity begins and strengthens the process of the laying down of myelin sheath around mature neuronal fibers, which functionally enhances the neural connectivity by increasing the speed of conduction of the electrical action potential down the axon length (Siegel, 2001). The assumption is that synaptic contacts are initially transient and require some type of confirmation for their continued survival, and if such confirmation is not obtained, synapses will be pruned

according to the developmental schedule or due to competition from confirmed synapses (Nelson, 2000).

In a study by DeBellis, et al. (1999), evidence was found to support an association between early childhood maltreatment and adverse consequences for brain development. Specifically, smaller brains were associated with an earlier age of onset of abuse. Furthermore, four additional studies have explicitly examined the age of onset of childhood maltreatment as a predictor of later psychopathology in childhood and/or adolescence, and found an association between early childhood maltreatment and deleterious long-term mental health outcomes (Bolger, Patterson & Kupersmidt, 1999; English, Graham, Litrownik, Everson & Bangdiwala, 2005; Kaplow, Dodge, Amaya-Jackson & Saxe, 2005; Keiley, Howe, Dodge, Bates & Pettit, 2001).

Some researchers have an opposing viewpoint, and theorize that younger children may be buffered against many of the phenomena that would produce distress in older children. Protective mechanisms in this regard may include less-developed cognitive abilities as well as the decreased propensity toward shame and egocentric thinking (Kaplow & Widom, 2007). Experience-expectant and experience-dependent processes provide a template for the existence of sensitive periods of development.

Experience-Expectant Processes

Evidence for experience-expectant processes have been established in regard to the primary visual cortex by the discoveries of Hubel and Wiesel, who laid the initial groundwork for much of our current understanding of the developmental plasticity of the brain (Espinosa & Stryker, 2012).

By closing one eye of a kitten during the first few months of life, this led to the lifelong irreversible loss of visually driven activity in the cortex through the closed eye, and a dramatic increase in the number of neurons responding best to stimuli presented to the open eye. However, prolonged eye closure in adult cats had virtually no effect. Subsequent anatomical tracing revealed that the imbalance of activity resulted in the actual loss of synaptic inputs from the thalamic regions representing the closed eye and expansion of those representing the open eye (Katz, 1999). The effects of monocular deprivation and the existence of critical periods have been subsequently described in primates, rabbits, hamsters, rats, mice, ferrets and other species of mammals (Baroncelli, et al. 2010).

The result of these experiments was the beginning of the proposal that there were periods of development where changes in the external environment can alter preexisting neuronal connections (Hooks & Chen, 2007). The additional result of these experiments was that the seemingly innocuous act of covering an eye also profoundly alters the physical structure of the brain only during the critical period (Hensch, 2005).

In humans, the capacity to perceive stereoscopic depth requires early experience with binocular vision (Fox, et al. 2010), and deprivation studies provide some of the most important evidence for critical or sensitive periods. In the event a child's visual system is corrupted somehow, such as being born with a cataract, or if the child is brought up in a dark room, then the child's vision will suffer (Nelson, et al., 2011). It is well known that disturbances such as disease, metabolic disturbances and malnutrition produce both structural and functional impairments in the development of the cerebral cortex if they

occur during periods of synaptogenesis. On the other hand, these same global conditions, when occurring in the older child or adult, do not seem to produce the same degree of impairment in both structure and function (Monk & Nelson, 2001).

Evidence concerning critical periods in visual or auditory processing are based on comparative studies involving considerable experimental control, and on human studies in which confounding variables can be monitored and controlled (Thompson & Nelson, 2001). In order to define sensitive or critical periods for humans, it is imperative to consider developmental trajectories of these brain regions in humans (Heim & Binder, 2011).

Experience-Dependent Processes

Experience-dependent processes are similar to experience-expectant processes in the way that environmental inputs actively contribute to brain structure; however, with experience-dependent processes, experiences are not predetermined, nor are synapses anticipating the experiences at any particular stage (Glaser, 2000).

It is well known that exposure to normal speech within the first year of life confers on an infant's ability to discriminate speech sounds and eventually correctly produce these sounds (Thompson & Nelson, 2001) and that learning and appropriate social interaction requires stimulation from the environment (Nelson, 2000). Another example of experience dependent processes can be seen by the protracted growth of white matter, as documented by a significant increase in size of a pre-motor related portion of the corpus callosum following prolonged and highly intensive practice with a musical instrument in young children. The increase in size of the white matter tract is

associated with an increase in axonal cingula and thickness of myelin sheaths (Berlucchi, 2011). In the developing cortex, spine pruning or stabilization are driven by normal somatosensory experience. Increased spine and synapse densities have been reported after rearing or training in enriched environments, and also after long-term sensory stimulation and deprivation (Holtmaat & Svoboda, 2009). In non-primate animal research, changes in brain morphology, specifically the hippocampus, have been documented in regard to those species who were involved in specific experience-dependent experiences compared to those who were not (Rozenweig, 1996; Clayton, 2001).

Maltreatment fits under experience-dependent processes because it involves the crucial role of early experience in guiding brain development in ways that make the individual more or less sensitive to possible threat in the environment and thus more or less likely to engage the stress system throughout life (Twardosz & Lutzker, 2010). The mechanism of action of experience-dependent process is proposed to occur through synaptic overproduction during the early years of life, which allows for the likelihood that the brain will develop properly within a positive rearing environment that will supply the necessary minimal amount of sensory stimulation to maintain necessary portions of the genetically created and highly dense synaptic circuitry (Siegel, 2001; Webb, et al. 2001; Chechik, et al. 1998; Fox & Rutter, 2010). This process is localized to the brain regions involved in processing information arising from the event experienced by the individual and involves formation of new synapses and/or the modification of existing ones (Belsky & De Haan, 2011). Interactions with attachment figures are essential during

this time to create contingent, collaborative communication necessary for the proper emotional, cognitive and social development of the child.

Experience-dependent processes are typically seen through the different effects on specific brain structure morphologies, function and gene expression of children who have been exposed to trauma and early life stress. Research with rats, non-human primates and other mammals have supported this notion (Lenroot & Giedd, 2011; Dannlowski, et al. 2012; McCrory, De Brito & Viding, 2010; Spinelli, et al. 2009; Mehta, et al. 2009; Creeden, 2004; McEwen, 2007; Blair & Raver, 2012; Szyf, 2012; McGowan, et al. 2008; Pechtel & Pizzagalli, 2011; Lakshminarasimhan & Chattarji, 2012; Roth & Sewatt, 2011; Lickliter, 2008; Nelson, Bos, Gunnar, Sonuga-Barke, 2011; Spinelli, et al., 2009; Bradshaw & Schore, 2007).

While recent empirical evidence suggests that there may indeed be critical periods for stress-related alterations in brain development, ultimately leading to greater long-term psychological disturbance (Kaplow &Widom, 2007), there are others who suggest that younger children may be buffered against many of the phenomena that would produce distress in older children. Given the strong evidence from neurobiological studies noted above, this paper will proceed forth from the perspective that children who experienced maltreatment and early life stress at an earlier point in their lives would demonstrate greater psychological problems throughout their lifetime than would children who were maltreated and exposed to early life stress later in life.

Resilience and Vulnerability

The following section will discuss the psychosocial, biological and genetic influences of resilience and vulnerability. Integration of attachment theory, the diathesis stress model, neurobiological stress, and critical periods of development will be integrated into this section, as they are all substantial components of resilience and vulnerability to psychopathology.

The Meaning of Resilience

The majority of empirical evidence on processes that link resilient attributes with positive outcomes has been based on examination of how children respond to extreme life stressors. Among the adverse conditions considered in the literature have been violence, maltreatment and abuse, natural disasters, poverty, parental psychopathology and war (Davis, Luecken & Lemery-Chalfant, 2009). In the overall field of resilience, standardized and operational definitions of resilience do not exist, even within the specific area of resilience research focusing on child maltreatment (Afifi & MacMillan, 2011).

Since the inception of the concept of resilience, major concerns about its construct have been raised as a result of ambiguities in its definitions, variations in inter-domain functioning and risk experiences among ostensibly resilient children, and instability in the phenomenon of resilience (Luthar, Cicchetti & Becker, 2000). However, as research in this has developed over time, the conceptualization of resilience has been refined, such that most researchers now recognize it as a dynamic process that results from ongoing interactions between a child and the environment, rather than an internal characteristic of

the child (Vanderbilt-Adriance & Shaw, 2008). This complex interplay includes the social context, nature, number, persistence and intensity of adverse events, (Herrman, et al. 2011), in addition to the balance and type of protective factors (Cicchetti & Rogosch, 2009).

Counterbalancing the effects of risk factors are what are commonly termed "Protective" or resilience factors, which enhance the individuals capacity for resilience (Harvey & Delfabbro, 2004). Among the array of protective factors that have been identified to promote resilient functioning in maltreated children are children's academic engagement, social competencies, average or above average intellectual performance, and the presence of a secure relationship with an adult caregiver (Cicchetti & Rogosch, 2009). It is agreed upon by researchers that the protective effects of resilience begins to be developed and acquired by emotional and secure attachments with parents, caregivers, or significant others (Broekman, 2011; Vanderbilt-Adriance & Shaw, 2008) during the beginning stages of life.

For children with a history of maltreatment, exhibiting competence across domains of functioning, such as behavioral, educational, and emotional functioning, appear to serve as evidence of resiliency (Walsh, Dawson & Matingly, 2010). Despite the lack of consensus regarding an operational definition, most use similar domains as evidence of resilience (Herrman, et al. 2011). While there have been improvements made in the conceptualization of resilience, challenges remain in establishing truly high risk contexts, interpreting the degree to which positive adjustment actually occurs in the context of chronic and severe risk, and determining the stability of resilience across time

and domains (Vanderbilt-Adriance & Shaw, 2008). Another issue, which has not been sufficiently discussed in the literature, is how we can best understand the interplay between the putative causes of the disorder and the clinically observed resilience seen in many children following such difficult experiences (Minde, 2003).

Epigenetics & Diathesis –Stress

From the time of the Greeks, philosophers and scientists debated over the origins of the structure and function of our species; while Aristotle argued that our origins and structure stemmed from nurture, Plato argued that they were rooted in nature (Lewkowicz, 2011). These divergent views ultimately gave rise to the nature-nurture dichotomy, which persists into modern day times, though it has become generally accepted that it is the interplay between genetic and environmental factors (G x E), also known as the epigenetic theory, causes differences in human cognitive and behavioral traits (Lenroot & Giedd, 2011).

The premise of epigenetic theory postulates that the external environment and experiences and internal environment of genetics have interweaving effects on each other, and argues that experience influences the cellular machinery of the gene, changing the expression of the gene (Fox & Rutter, 2010). It is important to note that environments cannot alter gene sequences, but genetic effects are dependent on the expression of genes (Rutter, 2010).

Of central importance to the epigenetic theory is diathesis-stress model, which postulates that some individuals are at heightened risk because of their genetic makeup of

succumbing to psychological disturbance when they encounter adversity, whereas others, are not so affected even when exposed to the very same adversity (Belsky, et al. 2006).

While many studies underline a strong association between child maltreatment and its immediate long term psychopathological consequences, clinical evidence points out that not all individuals exposed to maltreatment will develop psychopathological symptoms (Gillespie, Phifer, Bradley & Ressler, 2009). As a result, the variability in the individual responses suggests that this heterogeneity may be within the sphere of genetic and neurobiological factors (Bellani, Nobile, Bianchi, Van Os & Brambilla, 2012; Kim-Cohen & Gold, 2009). As advances in genetics, psychopharmacology and brain imaging permit a closer study of the biological underpinnings of resilience (Komaroff, 2005), the interplay of these factors require consideration into the critical question of why some children who are exposed to early life stress and maltreatment exhibit resilient behaviors in certain domains versus others who do not.

The regulation of gene expression through diathesis stress has been proposed as a potential molecular mechanism that can mediate maladaptations (vulnerability) as well as adaptations (resilience) in the brain (McCrory, et al. 2010), and can provide a potential explanation of the individual differences in response to environmental influences. It is believed that children exposed to environmental stressors known to increase risk for certain psychiatric disorders are at higher risk for that disorder if they carry particular gene variants, which renders them more susceptible to that stressor (Wermter, et al. 2010). It is postulated that these factors determine the degree of adaptability of the

neurochemical response system to new adverse exposures, as discussed earlier, as well as the function of the neural circuitry involved in stress responses (Feder, et al. 2009).

Gene x Environment studies have demonstrated that variation in specific genes moderates the impact of environmental risks on psychopathology (and vice versa), such that risk-exposed individuals who carry the protective variation of the gene have significantly reduced levels of psychopathology compared to comparably risk-exposed individuals with the vulnerable variant (Kim-Cohen & Gold, 2009).

Considerations of both the epigenetic theory and the diathesis stress model reflect the potential influence of early experience, particularly involving the interaction of the parent and child, on phenotypic development (Meaney, 2010), resilience and vulnerability. These approaches have grown from the observation that psychiatric disorders have environmental causes and that individuals show heterogeneity in their response to those causes, such as seen with the concordance of monozygotic twin studies with highly heritable disorders (Caspi & Moffitt, 2006), despite the fact that monozygotic twins share 100% of their genetic material. There has also been a failure to replicate direct effects of candidate vulnerability genes on specific psychopathological conditions, which suggests that genes may not influence behaviors directly, resulting in the examinations of gene and environment interactions (Belsky, Jonassaint, Pluess, Stanton, Brummett & Williams, 2009). It is also well known that the neonate cortex it neither localized nor very specialized at birth, thereby allowing the interactions with the environment to play a crucial role in gene expression and behavioral phenotypes

(Karmiloff-Smith, 2007), as discussed earlier by mechanisms such as synaptogenesis, differentiation and pruning.

Genes are a part of the developmental system in the same sense as the neural components, and are also susceptible to influence from other levels during the process of development (Gottleib, 1991). Recent work in developmental neuroscience and molecular biology have also made significant advances to which there is now evidence that early life experiences and environmental factors, (Roth & Sweatt, 2011; Masterpasqua, 2009) interact directly with genes in the developing brain, and provide insight into biological mechanisms whereby Gene x Environment interactions can biochemically alter genomic expression and thus influence differences in neural function (Meaney, 2010).

For example, the microneurodevelopmental processes involved during early development, such as cell proliferation, cell migration and differentiation, axon and dendritic growth and formation and synaptogenesis, occur as a result of gene regulatory networks (Fox, et al. 2010), while the environment has the ability to influence and alter the genetic programming of these microneurodevelopmental processes in either a negative or positive manner. The alteration of these microneurodevelopmental processes in turn alters the normal development of higher cortical regions of the brain, as these events are essential to the development of the functional architecture of the brain (Thompson & Nelson, 2010). The caveat is that crucial experiences must occur for the brain systems that underlie these behaviors to develop and function normally and for

behavioral and emotional development to proceed on a normal tract (Nelson, 2000). These epigenetic effects result in changes in gene expression; however, it is important to note that these effects are not changes in the sequence of base pairs, as in genetic mutations.

Deoxyribonucleic Acid (DNA)

To understand epigenetic effects, first it is essential to understand the structure of the genome.

DNA is wrapped around a complex of histone proteins and together they form clusters, known as chromatin. Chromatin facilitates the compaction of DNA (Biddie & Lightman, 2011). In order for DNA to be expressed, it must first come into contact both with enzyme RNA polymerase and transcription factors. Before this occurs, DNA must be unwrapped from the histone proteins, at which time the nucleic acid sequences are exposed and it is at this point that environmental factors can exert their epigenetic effects (Lewkowicz, 2011). Modifications of this packaging makes genes more or less available to the cell's chemical signals that determine whether the gene is expressed or silenced, and research has shown that genes on loosely packed DNA are more likely to be expressed than are those that are more tightly wound (Liekliter, 2008). Epigenetic changes are experience driven, semi-permanent alterations to portions of the DNA that can serve to either turn up or turn down expression of particular genes (Gunnar & Adam, 2012), and in germ cells can be heritable (Feder, et al. 2009).

In normal development, all the cells of an individual contain the same genome, which is capable of encoding multiple biological functions and gives rise to hundreds of

phenotypes, which arise from the selective expression of genes (Biddie & Lightman, 2011). Epigenetic changes play a significant role in normal cell differentiation by determining which genes will be turned on or off for each type of tissue. For humans and other mammals, the expression-specific genes are determined by the parent of origin; for certain genes, the copy derived from the mother is active while that emanating from the father is silenced, and in other cases it is the reverse. The silent copy is methylated in DNA regions that regulate gene expression and are thus inactive (Meaney, 2010).

During the normal developmental process, epigenetic factors play a role, such as with X-chromosome inactivation in human females (Masterpasqua, 2009), which occurs when one of the X chromosomes of the female's XX pair is downregulated. The epigenetic mechanisms that ensure the silencing of the X chromosome in this developmental process have been found to be through DNA methylation and histone modification. Epigenetic modifications through DNA methylation have also been identified in 26 forms of cancer, either by hypermethylation or hypomethylation (Masterpasqua, 2009). Again, these epigenetic processes are dynamic events that control the expression of genes without affecting the DNA sequence (Boulle, et al. 2012).

DNA Methylation

DNA methylation is the most relevant of the mechanisms for understanding the stability and plasticity of care giving effects (Jensen-Pena & Champagne, 2012), and has been the most studied with regard to understanding early life experiences and their neurobiological sequelae (Murgatroyd & Spengler, 2011).

Recent data in both animal and post-mortem human studies support the association of DNA methylation with early life stress and care giving experiences (Szyf, 2012), (Masterpasqua, 2009). Epigenetic regulation by DNA methylation imparts a memory of transcriptional states through modification of chromatin remodeling (Biddie & Lightman, 2011) and occurs by means of the addition of a methyl group to particular bases in the DNA sequence, which interferes with the chemical signals that allow a gene to be activated, thereby effectively silencing the gene (Lickliter, 2008). When cystones are not methylated, genes are expressed. The negative alteration of DNA methylation has been speculated to occur through environmental signals, by means of the biochemical stress response system (Meaney, 2010), and can result in long-lived but potentially reversible changes in gene expression.

To date, most of the Gene x Environment interaction studies involving childhood maltreatment regarding resilience and vulnerability have focused on the polymorphisms in monoamine oxidaise gene (MAOA) and serotonin transporter gene (5-HTT), two principal genes implicated in early brain maturation and the regulation of mood, behavior, and stress response (Kim-Cohen & Gold, 2009). DNA methylation of the brain derived neurotrophic factor gene and the human glucocorticoid receptor gene have also been of particular interest in regard to children who have been exposed to early life stress (Cole, 2013). All of the aforementioned GxE interactions have been linked with the physiological stress response system (Frigerio, et al. 2009; Mc Crory, DeBrito & Viding, 2010). It is important to note that while the idea of a direct causal link between one given gene and one psychiatric disease has been discarded, it is becoming increasingly clear

that a combination of several genetic factors can play a significant role in modulating the outcome of environmental influence (Claessens, et al. 2011).

Brain Derived Neurotrophic Factor Gene

The brain derived neurotrophic factor (BDNF) gene expression has been hypothesized as candidate through which early life experiences, specifically through care giving behaviors in early life, can modify brain structure and function, and play a role in resilience. Early life stress plays a crucial role in the remodeling of chromatin in the brain, and contributes greatly to the regulation of BDNF as it can repress the transcription and function of BDNF (Gomez-Pinilla, Zhuang, Feng, Ying & Fan, 2011; Meaney, 2010).

The same chronic stress that elicits hippocampal dendritic atrophy also reduces levels of BDNF in the rat hippocampus (Lakshminarasimhan & Chattarji, 2012), and has also been found to be reduced in rats who have been separated from their mothers (Komaroff, 2005). Evidence suggests that BDNF levels are reduced in mood disorders, by protecting against stress-induced damage and might affect neurogenesis in the hippocampus (Furmanga, Carreno & Frazer, 2012).

The downregulation of BDNF via DNA methylation is one of the neurobiological changes which is hypothesized to occur as a result of acute stress (Elzinga, et al. 2011). Decrease in serum BDNF levels were observed in major depressed patients when compared to healthy controls, several antidepressant medications have shown to increase BDNF levels, and correlations have been found between severity of depression and

BDNF levels (Lang, et al. 2006), which is also associated with early childhood maltreatment (Twardosz & Lutzker, 2010).

The importance of neurotrophins in supporting the survival of developing neurons became evident as a result of many studies, which demonstrated that neurotrophin stimulation is required to keep the survival of developing neurons alive in cell cultures. Withdrawal of neurotrophins led to apoptosis of these cultured neurons, recapitulating the necessity of neurotrophins in the inhibition of developmental apoptosis (Cheung & Ip, 2008).

The neuroprotective properties of neurotrophins stem from the binding of these proteins to their receptors and subsequent activation of intracellular signaling pathways that lead to activation of pro-survival pathways and/or inactivation of pro-apoptic signaling (Alcala-Barraza, et al. 2010). BDNF controls neuronal survival, differentiation and synaptogenesis, plays important roles in activity dependent forms of synaptic plasticity in the central nervous system, and modulates growth and complexity of dendrites and changes spine density and morphology (Carvalho, Caldeira, Dantos & Duarte, 2008), and is highly expressed in limbic structures in the cerebral cortex. BDNF is also important for long-term potentiation and neurogenesis (Boulle, et al. 2012).

Though there are several different types of neurotrophins, BDNF is the most abundant neurotrophin in the central nervous system related to synaptic plasticity (Andero & Ressler, 2012), and is a potent regulator of morphological plasticity of dendrites in various brain regions (Lakshminarashimhan & Chattarji, 2012).

Glucocorticoid Receptor Gene

DNA methylation has also been found to regulate the human glucocorticoid receptor gene (Marshall & Kenney, 2009; Roth & Sweatt, 2011), through means of the biological stress response system, and play a role in resilience.

Differential glucocorticoid responsiveness causing changes in synaptic plasticity are believed to underlie the vast array of neuroendocrine, behavioral and cognitive alterations (Claessens, et al. 2011). For example, during times of elevated stress, glucocorticoids are secreted and bind to glucocorticoid receptors and which are sensitive to circulating glucocorticoids. The function of the glucocorticoid receptor is to bind to glucocorticoids (cortisol) and once it does, it enters the nucleus where it regulates gene transcription involved in the body's response to stress (Lewkowicz, 2011).

Glucocorticoid receptor expression in the hippocampus influences the stress responsiveness of the HPA by participating in the feedback control mechanism that dampens the response of the HPA axis in response to stress. This results in fewer glucocorticoid receptors being made, and because these receptors are key in initiating the cascade of events that put the breaks on the stress response, the result is increased stress reactivity (Weder & Kaufman, 2011). Receptor binding is known to alter methylation and modify chromatin accessibility (Biddie & Lightman, 2011), which is the mechanism by how the early life stress response system regulates the glucocorticoid receptor gene.

Both animal and human studies have correlated negative early care giving experiences with a decrease in glucocorticoid receptor expression in the hippocampus (Tyrka, et al. 2012; Claessens, et al. 2011; Meaney, 2010; Szyf, 2012). The decrease in

glucocorticoid expression increases the amount of adrenocorticotrophic releasing hormone (ACTH) in the hypothalamus, which in turn results in more ACTH from the pituitary and more cortisol from the adrenal glands (Masterpasqua, 2009).

Methylation of the glucocorticoid receptor has been implicated in several studies of individuals with a history of childhood abuse (Yang, et al. 2013), and two independent studies in individuals with a history of early childhood abuse showed an association between suicide completion and methylation of the glucocorticoid receptor gene (Weder, et al. 2014).

There is evidence for decreased hippocampal glucocorticoid receptor expression in several psychopathological conditions associated with suicide, including schizophrenia and mood disorders. Suicide is also strongly associated with a history of childhood abuse and neglect, and this effect is independent of that associated with psychopathology (McGowan, et al. 2009). Animal studies investigating negative early care giving experiences is linked to increased methylation, which downregulates glucocorticoid receptor gene expression in the hippocampus as a result of the inaccessibility of transcription sites, which ultimately results in decreased glucocorticoid receptors in the hippocampus.

Serotonin Transporter Gene

The functional polymorphism in the promoter region of the serotonin transporter gene (5-HTT), which has been termed the 5-HTT gene-linked polymorphic region (5-HTTLPR), is a highly investigated gene variant (Feder, et al. 2009; Belay, et al. 2011),

due to the fact that it is involved in the reuptake of serotonin at brain synapses (Caspi, et al. 2003).

This genetic polymorphism can result in individuals who either have a short or long allele of the serotonin transporter gene, as those with the short variation produce less transporter protein while those with the long variation produce more of it (Lewkowicz, 2010). The serotonin transporter (5-HTT) is located at the presynaptic membranes of the serotonergic nerve terminals where it performs sodium-dependent transport of the neurotransmitter serotonin from the synaptic cleft back to the nerve terminal, thus limiting the action of serotonin to a short period after its release (Uher & McGuffin, 2008). This polymorphism has been associated with increased HPA axis activity, increased neuronal activity in amygdala fear pathways and decreased gray matter volume in the amygdala and frontal cortex (Claessens, et al. 2011).

In two reports, a history of childhood abuse was associated with increased methylation in lymphoblast DNA in the promoter region of the serotonin transporter gene (Yang, et al. 2013). Individuals with the short variation show more impulsivity following deprivation or abuse in multiple species (Kinnally, et al. 2010), and are more biologically reactive to stress. The short variation has also been linked with higher cortisol levels in response to stress tasks in children (Frigerio, et al. 2009).

Some human and animal studies have shown that individuals with the long variant were less likely to become depressed subsequent to stress (Komaroff, 2005), and had less suicidality subsequent to stressful life events or childhood maltreatment (Kim-Cohen & Gold, 2009), while other studies have not directly associated the 5-HTT gene with

depression, but as a moderator of the serotonergic response to stress (Caspi, et al. 2003). Altered serotonin transporter expression early in life may moderate the effects of early life stress and influence emotional development (Kinnally, Capitanio, et al. 2010).

Monoamine Oxidase-A Gene

There is also growing evidence that the polymorphism of the monoamine oxidase-A (MAOA) gene has been associated with a variety of aversive early childhood experiences (Belsky, et al. 2009), including childhood maltreatment and psychopathology (Kim-Cohen & Gold, 2009) by means of the physiological stress response system (McCrory, et al. 2010), and also influences resilience.

MAOA is a mitochondrial enzyme responsible for the degradation of a variety of biogenic amines, such as the neurotransmitters dopamine, norepinephrine, and serotonin (Cicchetti & Rogosch, 2009), following reuptake from the synaptic cleft. Several human studies have been found to determine its efficiency in the metabolizing of these neurotransmitters (Herrman, et al. 2011). The mechanism by which the MAOA enzyme degrades the neurotransmitters is through oxidation, and ultimately results in the reduction of circulating neurotransmitters in the brain (Lewkowicz, 2011), and therefore plays a key role in regulating behavior.

A polymorphism in the promotor region of the MAOA gene is known to affect gene expression (Kim-Cohen, et al. 2006); the length of this polymorphism determines the efficiency with which MAOA is transcribed and ultimately produced within individuals (Cicchetti & Rogosch, 2009). The high activity MAOA version of the gene is associated with resilience, whereas the low activity MAOA version is associated with

risk, if exposed to aversive early childhood experiences. In several human studies, maltreated children whose genotype expressed low levels of MAOA expression had higher levels of conduct disordered behaviors, antisocial and aggressive behaviors (Harvard Mental Health Letter, 2006; Wermter, et al. 2010; Kim-Cohen, et al. 2006) and have been linked to aggressive behaviors in non-human primates (Lewkowicz, 2011).

Making the Connection

The common denominator of the above-mentioned gene x environment interactions and attachment-disordered behaviors is the pervasive, overstimulation of the physiological stress response system, which results in potential changes in gene expression, brain morphology, neurochemical functioning and resilience.

In tandem with this concept as well as the concept of diathesis stress, attachment theory argues that developmental processes can best be understood as the product of the interaction of a unique genetic endowment with a particular environment (Schore, 2001b). In the presence of maltreatment, these variants may be the adaptive, resilience-promoting attributes (Kim-Cohen & Gold, 2009). Children who are exposed to early life stress and maltreatment, and who present with disorders of attachment, are relating to others in ways and behaving in ways which are perceived by that individual to promote emotional safety, even if the perceived or real threat is no longer present.

It is suspected that susceptibility markers would not have emerged, survived and spread across a substantial minority of the population if they did not advance adaptation to at least some ecological niches for at least some individuals (Ijzendoorn, Belsky & Bakermans-Kranenburg, 2012). Even though the risk variants constitute a high-risk

strategy, which jeopardizes the individual's health and survival, these developmental adaptations to high stress environments and lack of attachment enable them to endure in an inept situation (Ellis, Boyce, Belsky, Bakermans-Kranenburg & VanIjzendoorn, 2011).

While much of the variability in the resilience research is poorly understood (Gillespie, et al. 2009), it underscores the potential importance of intrapsychic variables, such as internal working models of attachment theory, as the meaning of events are crucial to emotional responses (Gilbert & Miles, 2000).

Neuropsychology of Internal Working Models

Environmental triggers are not objective events, as their impact is mediated through the subjective experience of the child (Atwool, 2006), and can also play a significant role in regulating gene expression profiles (Cole, 2013), and neurochemical response.

The concept of non-shared environments, which is any environmental experience whether perceived or actual, which differs from siblings growing up in the same family, has been extensively researched in an attempt to gain further clarity into differential outcomes. Research in this area suggests that these different experiences, and perceptions of experience, appear to play a role in the development of maladaptive or adaptive behavior (Sheehan & Noller, 2002), and may be a function of attachment (Fonagy, 2003) through internal working models (Fearon, Bakermans-Kranenburg, Ijzendoorn, Lapsley & Roisman, 2010) postulated by traditional attachment theory.

Bowlby and subsequent attachment researchers suggested that the recurrent nature of infants experiences lead to the development of internal working models of the self and others, generalized representations of events, that influence the infants emotional expectations (Beebe, Lachmann, Markese & Bahrick, 2012). This cognitive-affective representation of the self is thought to become generalized over time and influence functioning in wider interpersonal relationships across the life span, and form the basis of a generalized sense of the self as worthy of love and care and others as available and responsive (Steele, 2004). While traditional attachment theory posits that internal working models are mostly stable over time, they also have the potential to change in response to a substantially changed care-giving environment.

Little data are available regarding the degree of recovery of attachment following early childhood maltreatment because most current studies have focused on children adopted out of institutions (Hornor, 2008). On the other hand, it has been shown that attachment security can be subject to change and alterations with regard to external life event impacts, as studies have shown that Bowlby's hypothesis with regard to continuity and discontinuity of attachment security has been demonstrated (Svanberg, 1998). A large empirical body of literature has documented that variations in social interactions in the first months, which general infant expectancies of recurrent events, predict later social and cognitive outcomes (Beebe, et al. 2012). While there have been studies conducted that have documented this, there is a large difference in length of follow up, among other factors, which make direct comparisons very difficult (O'Connor, Bredenkamp & Rutter, 1999).

In the same context, adoptive and foster families have been the subjects of a great deal of interest, as these placements appear to be natural experiments in relation to continuity of internal working models. According to Pace, Zavattini & D'Alessio (2012), studies of children placed prior to 12 months of age have showed the ability to almost completely catch up with non-adopted children in terms of their cognitive, behavioral, relational and affective development and attachment security. Supporting this notion, an extensive amount of research on early individual differences in attachment security attests that infants intuitively sort out who is emotionally dependable and how, by 12 months of age, if not earlier (Allen, 2012). Studies show that children adopted after 12 months of age, and have therefore experienced at least one rupture in their primary attachment, have shown difficulties in their emotional and cognitive catch up (Pace, et al. 2012), supporting the stance of the attachment theory's internal working model.

Where a large body of evidence documents the role of care giving sensitivity in predicting, and even causally influencing attachment security, the specific role of the internal working model has been less subject to empirical scrutiny, often being used primarily as an interpretive heuristic in accounting for discerned relations between early attachment and later psychological functioning (Belsky & Fearon, 2002). As children develop and are better able to provide protection for themselves, the threshold and need for overt secure base behavior diminishes. Despite this reduction in secure base behavior, attachment is not relinquished (Weinfield, et al. 2004).

In regard to personality and temperament characteristics, there is little known about the possible temperamental or personality variables which may be helpful in

protecting the attachment system in children who have been exposed to pathogenic care (Minde, 2003). While there is varying evidence of an association between specific attachment patterns and some indices of temperament, the four main classifications of attachment are unlikely to be determined by a single property of the child such as temperament (Steele, 2004).

Implicit Memories

Internal working models are thought of as the building blocks of emotion regulation that the infant and child accommodate into their own regulatory system, which then become anchored in the infant's neurochemical and physiological makeup.

Memory is one of the mechanisms by which past experience is encoded in the brain and shapes present and future functioning, and is closely aligned with internal working models. For the first year of life, the infant only has available an implicit form of memory, which includes emotional, behavioral, and perceptual forms of memory, the generalizations of repeated experiences (schemas), and early attachment experiences (Kay, 2009). When implicit memories are activated, they do not have an internal sensation that something is being recalled; they merely influence emotions, behaviors and perceptions, directly, in the here and now, without awareness of their connection to some experience in the past (Siegel, 2001).

Between two and three years of age, children begin to develop explicit memories, which involves processes largely in conscious awareness (Corbin, 2007), in tandem with Bowlby's hypothesis that around the age of three, behaviors signifying a goal-corrected

partnership begin to emerge, which mediate internal working models (Fonagy, 2003). It is believed that early implicit memory, different from the processes in later development, forms enduring rules and prototypes that exert perpetual influence in interpreting subsequent experience (Corbin, 2007).

The hippocampus is necessary for awareness of explicit memories, where the amygdala is the portal for experiencing emotions, and also influences perceptions by assigning emotional value to implicit and explicit memories. In regard to internal working models, the amygdala system records the implicit memories without cognitive remediation through the cortex, which explains why individuals often have sensations to places, persons and stressful situations related to stressful events and have no idea why (Kay, 2009). Therefore, in RAD, enduring rules exist in implicit memory structures and are not available for conscious reflection, thought and related processes (Corbin, 2007), resulting in difficulties in changes of internal working models over time.

Mirror Neurons

The idea that individuals possess internal working models of attachment interrelates with broader research in cognitive neuroscience and social cognition (Dykas & Cassidy, 2011).

In studies on monkeys, it was observed that when a researcher was holding a piece of food, its motor neurons fired in the same way they did when the monkeys themselves grasped the food. The researchers concluded that the pattern of neuron activity associated with the observed action was a true representation in the brain of the

act itself, regardless of who was performing it (Divino & Moore, 2010). These neurons were subsequently dubbed mirror neurons.

Research on mirror neurons has recently posited that there is a biological basis of non-verbal communicated emotion and empathy, and may be optimally developed in secure attachment relationships (Allen, 2012). Scientists think that this capacity for neural mirroring helps us interpret other individual's actions and feelings (Divino & Moore, 2010), and may be another mechanism by which internal working models function.

Treatment Strategies

In this section, attachment based and psychotherapeutic and psychoeducational treatment modalities will be discussed. It is beyond the scope of this paper to consider and discuss all of the various interventions that have been proposed and studied, so a focus will remain on the therapies that have specific training protocols and processes (Zeanah, Berlin & Boris, 2011). Controversial non-attachment based interventions will also be briefly discussed.

Attachment Based Interventions

Traditional attachment theory holds that caregiver qualities such as environmental stability, parental sensitivity, and responsiveness to children's physical and emotional needs, consistency, and a safe and predictable environment support the development of healthy attachment. Bowlby believed that attachment theory had particular relevance for psychotherapy in that the chief role of the therapist is to provide the patient with a temporary attachment figure. He felt that doing so would, "Provide the patient with a

secure base from which to explore both himself and also his relations with all those with whom he has made or might make, an affectional bond" (Levy, 2013). From this perspective, therapy for children who are maltreated and described as having attachment problems emphasizes providing a stable environment and taking a calm, sensitive, non-intrusive, non-threatening, patient, predictable and nurturing approach toward children (Chaffin, et al. 2006).

There is compelling evidence that children suffering from attachment- related problems can benefit from a single warm and stable relationship, and it does not seem to matter whether the relationship is with a parent, teacher, family friend, volunteer, etc. (Hauggard & Hazen, 2004). While it is known in the field that psychotherapy changes the brain by forming new neural connections through concurrent processes of attachment and new learning (Corbin, 2007), there have not, however, been prior studies that investigate empirically how the properties of attachment are manifest in therapy relationships (Parish & Eagle, 2003).

Compared with older children, young children depend more on their primary attachment figures, encounter fewer external influences and demands, and exhibit less rigidly formed internal working models that are more open to influence. Attachment interventions might therefore be more straightforward and powerful for younger children because of the greater direct influence of the attachment system (Zilberstein, 2011). On the other hand, other research has found that some children who have been emotionally neglected early in life have enduring attachment problems throughout development and

have been insensitive to any replacement experiences, including therapy (Corbin, 2007; Ippen, Harris, VanHorn & Lieberman, 2011).

As discussed earlier, RAD shares many symptoms with disorders that are common among children, including conduct disorder (Haugaard & Hazan, 2004), due to the externalization of behaviors. Although parents of children with conduct disorder are often distressed about the strained relationships they have with their child, this is not the primary concern of interventions for children with disorders of attachment (Barth, Crea, John, Thoburn & Quinton, 2005), and attachment related interventions should not be intermixed with conduct disordered children.

To date, there are no current evidence-based interventions for children with attachment disordered behaviors (Boekamp, 2008; O'Connor & Zeanah, 2003), and there are no randomized clinical trials to date designed to evaluate the utility of a treatment specifically targeting RAD (Buckner, et al., 2008). Adding to these complexities, many current treatment approaches that are utilized are not systematic or researched driven, or even theoretically coherent (Marvin & Whelan, 2003), and not much is known about the long-term effects of these interventions (Kalinauskiene, et al. 2009).

Despite these difficulties, there are a few attachment-based interventions that do exist and have shown some efficacy, such as the Dyadic Developmental Therapy for children over 5 years of age, and Child-Parent Psychotherapy, Circle of Security, and Video Based Intervention to Promote Positive Parenting for children 5 years of age and younger (Zilberstein, 2011; Becker-Weidman & Hughes, 2008; Toth & Gravener, 2012). It is important to note that these interventions are not employed only in the case of

attachment disorders, but rather to support the development of child-parent attachment in high risk conditions and/or to address concerning parent-child interactions and relationship disturbances (Zeanah, et al. 2011).

The availability of a caring and stable caregiver is one of the most important factors that distinguish abused and neglected individuals with good developmental outcomes form those with problems (Weder & Kaufman, 2011); therefore, all of the following attachment based therapies aim to readdress child-parent relational difficulties and help with the development of more secure attachments (Hardy, 2007). Numerous others exist that appear to be based on attachment theory; however, upon review of the research, they are not backed up by many studies, if any, or randomized controlled trials.

D**yadic Developmental Therapy (5 years- Adolescence)**

In Dyadic Developmental Therapy, the basic tenant is to focus on parenting strengths as reflected in observed moments of caregiver-child engagement. The treatment seeks to remediate the internal working models that have several important and overlapping dimensions: modeling the healthy attachment cycle, reducing shame, experiencing safe and nurturing physical contact that is containing, and the interpersonal regulation of affect (Becker-Weidman, 2006). Once trust is built through positive reinforcement of the caregiver, the therapist can point out and process moments of frustration and disengagement and begin to reshape the interactions (Boris & Zeanah, 2005).

Eye contact, touch, tone of voice, facial expressions and gestures are all central to this intervention, as the non-verbal aspect of Dyadic Developmental Therapy is crucial

for this population due to some trauma taking place prior to the maturation of explicit memory. According to Becker-Weidman & Hughes (2008), other reasons why this treatment intervention is primarily non verbal is because the traumas experienced by these children were primarily non-verbal as well, in the form of harsh and abusive looks, touch, as well as failure to respond to or initiate support when the child was in distress. Evidence is accumulating that demonstrates the infant's autonomic nervous system requires the mother's (or a caregiver's) autonomic nervous system for dyadic regulation in order to go on and learn how to self-regulate (Quillman, 2012). Essentially, with this mostly non-verbal approach to treatment, it is hypothesized that these positive non-verbal interactions will help the child regulate emotions associated with traumatic memories and develop new internal working models in an effort to facilitate a resolution.

Though Dyadic Developmental Therapy is used with biological parents as the parent's insensitivity is suspected to be the cause of the child's difficulties, foster and adoptive parents who may not be the cause of the child's difficulties may also be involved in this type of treatment as it is presumed the child has not developed a selective attachment relationship to them (O'Connor & Zeanah, 2003).

Two recent outcome studies have provided support for the efficacy of Dyadic Developmental Psychotherapy with populations who have disorders of attachment (Becker-Weidman & Hughes, 2008).

Child-Parent Psychotherapy (Infant-5 years)

The link between Child-Parent Psychotherapy and attachment theory is the emphasis on emotional communication and the defensive processes that threaten to

distort it (Zeanah, et al. 2011). Child- Parent Psychotherapy integrates modalities derived from psychodynamic, attachment, trauma, cognitive behavioral and social learning theories (Lieberman, Ippen & Van Horn, 2006).

In this type of intervention, the focus is on the relationship between the caregiver and child. Through dyadic sessions, the therapist utilizes the child's spontaneous play and naturally occurring interactions between the parent and child as a vehicle for understanding maladaptive relational patterns and as a catalyst for change (Toth & Gravener, 2012). Whether or not trauma related themes are evoked during sessions, the therapist is able to translate the meaning of the child's actions, thoughts and feelings to the caregiver, provide interpretations of the meaning of the child's and parents behavior as they arise in the context of play, and model more effective meanings and ways of interacting with the child in a developmentally appropriate and emotionally sensitive manner (Lieberman & Van Horn, 2009).

Links are explored between the caregiver's early childhood experiences and their current feelings, perceptions, and behaviors towards their children, as well as a focus on the parents' current stressful life circumstances and culturally derived values (Zeanah, et al. 2011). Individual sessions with the caregivers are employed in circumstances in which a judgment is made that fostering a caregivers development independent of the child is necessary (Lieberman & Van Horn, 2009).

Current research on Child-Parent Psychotherapy provides support for the efficacy of this intervention (Toth & Gravener, 2012) in decreasing behavior problems and symptoms of PTSD among children and their mothers in a culturally diverse, low income

group of preschoolers exposed to marital violence and their battered mothers (Lieberman, et al. 2006).

Circle of Security (Infant-5 years)

The Circle of Security was developed as an intervention to enhance attachment relationships between infants and young children and their caregivers, primarily through work with the caregivers, and contains both therapeutic and educational components (Zeanah, et al. 2011). This intervention utilizes each child's attachment classification coded from the Strange Situation, along with the mother's attachment-related behaviors and representations, as the basis for formulating an individualized approach for each dyad (Hoffman, Marvin, Cooper & Powell, 2006).

This intervention protocol assumes that children with problematic attachments miscue their caregivers regarding their underlying attachment and/or exploratory needs in the moment (Marvin & Whelan, 2003). As in most non-secure patterns, both the child and the parent miscue each other, and accept each other's miscues. Using a circle to show how the child depends on caregivers both as a secure base to support exploration and as a safe haven that regulates distress, the intervention looks individually at dyads to help caregivers better learn to implement those goals through sensitive responsiveness (Zilberstein, 2013).

There are preliminary data on the Circle of Security, which support the efficacy of this intervention for populations who require enhancement of attachment relationships with their caregivers (Zeanah, et al. 2011).

Video Based Interventions to Promote Positive Parenting (Infant-5 years)

Video Based Interventions to Promote Positive Parenting have been based on the premise that parental security is a determinant of children's attachment security and can be defined as the ability to accurately perceive the child's signals and to respond promptly and adequately to these signals (Groeneveld, Vermeer, Ijzendoorn & Linting, 2011).

This intervention is a brief home based attachment intervention delivered in four home visits, and attempts to promote maternal sensitivity through interveners presentation of written materials and review of in-home videotaped caregiver-child interactions (Zeanah, et al. 2011). Goals of this approach include helping the caregiver understand the child's comfort seeking and exploratory behaviors, accurately decoding and responding to the infant's signals, and empathetic communication (Zilberstein, 2013).

Studies using this approach showed positive effects on parental sensitivity and/or attachment security in nonclinical groups, and in at-risk and clinical groups, and with mothers with eating disorders and their infants (Van Zeijl, et al. 2006)

Non- Attachment Based Interventions

There are several non-attachment based interventions, which vary in their use of techniques, and are under the classification of "Attachment Therapy". These interventions involve several techniques include Rebirthing, Holding Therapy, and Therapeutic Parenting.

A substantial amount of clinical writing about attachment-based therapies regards the child as the primary target of intervention. Therapists who employ these techniques also hold the notion that children with attachment problems actively avoid forming genuine relationships, and consequently relationship-based interventions, such as those cited above in the attachment related interventions section, are unlikely to be effective (Chaffin, et.al, 2006). The central tenant of these therapies are establishing total adult control, demonstrating to the child that he or she has no control, and demonstrating that all of the child's needs are met through the adult.

The treatment of RAD in regard to these interventions is based on the assumption that the child has repressed rage resulting from earlier negative experiences that interferes with the ability to form an attachment (Barth, et al. 2005). This theory appears to be rooted almost exclusively in observation rather than in science or traditional attachment theory, and is not considered well supported by most attachment researchers. Additionally, it is questionable as to whether releasing rage is actually beneficial. In fact, empirical evidence indicates that venting anger may actually increase anger and aggression (Buckner, et al., 2008).

In addition to the lack of empirical support for attachment therapies and fact that studies in attachment therapies have relied on measures of general behavioral/emotional problems as the index of response rather than measures of attachment (O'Connor & Zeanah, 2003), numerous mental health professionals and professional societies warn against the use of these therapies (Chaffin, et al. 2006).

Due to the strong potential for misuse and misapplication, along with the fact that these techniques are ethically questionable, the US Office for Victims of Crime released treatment guidelines that single out holding therapy as the one intervention mote likely to do harm than good (Barth, et al. 2005). The count is uncertain; however, five or six child deaths seem to have occurred at the hands of parents following the advice of attachment therapy practitioners. These deaths most often resulted from asphyxiation. In one case, the child died when her adoptive father lay on her with the full weight of his body; in one, the child was restrained with duct-tape in a high chair with her mouth covered; in another, the child died of hyponatremia after she was forced to drink large quantities of liquid as a punishment for disobedience (Mercer, 2004).

Proponents of these various attachment therapies argue that these techniques present no physical risk to the child if done properly, describe their approach as nurturing, and dispute that any of their interventions involves coercion or involuntary restraint. The primary evidence offered by proponents to support these arguments is anecdotal report, patient testimonials, therapist observations and their own clinical experience of appearing to achieve success in cases where prior treatment has failed (Chaffin, et al. 2006).

Holding Therapy and Rebirthing

Holding is thought to provide the child with an experience of safety and security that is contrary to previous experiences of severe abuse and neglect (O'Connor & Zeanah, 2003), and includes the use of a variety of coercive techniques including rib cage stimulation (pinching, tickling, knuckling and/or licking). Children may also be held

down, may have several adults lie on top of them, or their faces may be held so they can be forced to engage in prolonged eye contact (Chaffin, et al. 2006).

Rebirthing refers to a procedure in which the child is wrapped tightly into blankets, covered with pillows, and held by several adults who push on the pillows in imitation of uterine contractions (Mercer, 2001). During these interventions, the parents may be present in the room or on a video monitor.

Therapeutic Parenting

As a part of therapeutic parenting, caregivers may be counseled to keep their children at home, bar social contact with others beside the caregiver, favor home schooling, assign children hard labor or meaningless repetitive chores throughout the day, require children to sit motionless for prolonged periods of time, and insist that all food and water intake and bathroom privileges be totally controlled by the parent (Chaffin, et al. 2006).

With this type of intervention, children may not be allowed to speak until spoken to, and if they speak, they must be required to hold their hand over their mouths for 5-15 minutes. Each action the child engages in which is not in compliance with the caregiver's requests, there is a punishment.

In addition to the assertion of power, therapeutic parents are expected to use nurturing tools such as touch, smiling, hugs, and snuggling with the parent chooses to give them, whether the child asks for them or tries to reject them (Mercer, 2001).

Psychopharmacological Interventions

Currently, no psychopharmacological intervention trials for Reactive Disorder have been conducted (Boris & Zeanah, 2005; NIMH, 2012), and there is no literature supporting the use of pharmacological treatment to address the core attachment deficit (Weibnerg, 2009) as seen in RAD.

Upon review of the National Institute of Mental Health website (NIMH, 2012), there are no sections discussing pharmacological interventions or options for RAD or disorders of attachment. The American Academy of Child and Adolescent Psychiatry (AACAP, 2011) notes that the signs and symptoms in children with RAD may also be found in other psychiatric disorders; however, no specific disorders are noted, and parameters for the prescribing of psychotropic medications in this population are non-existent. Contrastingly, psychotropics are noted to be an option for the treatment of co-morbid conditions associated with RAD (Mayo Clinic, n.d).

As noted earlier in this paper, there are few direct data available about disorders that may be co-morbid with RAD (Boris & Zeanah, 2005) and the DSM-IV-TR does not indicate any diagnoses that may be co-morbid with RAD (DSM-IV-TR, 2000). On the other hand, it is well documented that in children who have been exposed to pervasive early life stress, externalization of problems appear to predominate during childhood, whereas substance abuse and affective disorders are observed during adulthood (Gunnar, Fisher, and the Early Experience, Stress & Prevention Network, 2006). Because children with disorders of attachment have impaired affect regulation, stress regulation and behavioral modulation, it can postulated that children with these symptoms who have

RAD are prescribed medications for the externalization of behaviors, which can easily be misdiagnosed, and psychopharmacologically treated as, Conduct Disorder and/or Oppositional Defiant disorder (Chaffin, et al. 2006).

In regard to Conduct Disorder, The American Academy of Child and Adolescent Psychiatry (AACAP, 2013a) notes that psychotropic medications that are typically prescribed for conduct disorder are those used to treat the "Underlying and associated medical conditions such as ADHD, depression, bipolar disorder, and anxiety". Similarly with Oppositional Defiant Disorder, it is noted that psychotropic medication may be "Helpful in controlling some of the distressing symptoms, as well as the symptoms related to co-existent conditions such as ADHD, anxiety and mood disorders" (AACAP, 2013b).

Because the conditions of ADHD, ODD, Conduct Disorder, Anxiety Disorder and Depressive Disorders frequently co-exist with each other (Bonati & Clavenna, 2005), this opens the classes of drugs for both Conduct Disorder and Oppositional Defiant Disorder along with their potential co-morbidities, to be the following: anxiolytics, beta blockers, stimulants, mood stabilizers, antidepressants, anti-convulsants and atypical antipsychotics, all of which can have a wide range of adverse side effects.

In treating depression, the most popular types of antidepressants are selective serotonin reuptake inhibitors (SSRI's), and other types are selective norepinephrine reuptake inhibitors (SNRI's) and monoamine oxidaise inhibitors (MAOI's), and side effects can include headache, nausea sleeplessness or drowsiness, agitation, sexual problems, dry mouth, constipation, bladder problems and blood pressure problems. In

2005, the U.S Food and Drug Administration (FDA) adopted a black box warning on antidepressants for children and adolescents, citing an increase in suicidal thinking or attempts (NIMH, 2012).

For Bipolar Disorder, medications typically prescribed are mood stabilizers such as Lithium, anticonvulsants such as Depakote, Tegretol, Lamictal and Trileptal and various atypical antipsychotics, including Risperidone, which is the most frequently used atypical for treating childhood aggression (Leonard, 2012).

Side effects of Lithium include loss of coordination, excessive thirst, frequent urination, blackouts, seizures, slurred speech, fast, slow, irregular or pounding heartbeat, hallucinations (visual and/or auditory), changes in vision, itching, rash, and swelling to eyes, face, lips, tongue, throat, hands, feet, ankles or lower legs. Possible side effects linked with Depakote include changes in weight, nausea, stomach pain, vomiting, anorexia, loss of appetite, damage to the liver or pancreas, increased risk of suicidal thoughts or behaviors and increase in testosterone and polycystic ovarian syndrome in teenage girls (NIMH, 2012).

Adverse effects of atypical antipsychotic medications are weight gain, diabetes, hyperlipidemia, prolactin and sexual function, cardiac problems and extrapyramidial symptoms such as dystonia, akathisia, Parkinsonism and tremor (Bebarta, Kostic & Gonzalez, 2005). Extrapyramidial symptoms can cause patients distress, impair quality of life, cause stigma, and in severe cases lead to secondary morbidity and even mortality

(Haddad & Dursun, 2008). The FDA also adopted a black box warning on atypical antipsychotic use in children.

In regard to medications prescribed for anxiety disorders, medications typically prescribed are anxiolytics such as benzodiazepenes and beta-blockers such as Buspar. Side effects of benzodiazepenes include upset stomach, blurred vision, headache, confusion, grogginess and nightmares.

Potential side effects from beta- blockers include dizziness, headaches, nausea, nervousness, lightheadedness, excitement, trouble sleeping, fatigue, cold hands, dizziness, weakness, and can worsen symptoms of asthma and diabetes (NIMH, 2012).

In treating ADHD, medications commonly prescribed include stimulants, and in 2002, the non-stimulant medication Strattera. Side effects include decreased appetite, sleeping problems, stomachaches, headaches and tics (NIMH, 2012). Other less commonly, but potential side effects include psychosis, mania, aggression, cardiovascular problems (NIMH, 2012).

Of the psychotropic medications listed above as treating Conduct Disorder and Oppositional Defiant disorder, along with their co-morbidities (depression, mood disorders, ADHD and anxiety related disorders), most are not FDA approved for use in children and adolescents, have no parameters regarding pediatric dosaging, and those that are approved for children and adolescents have serious, potentially life threatening side effects, including death, (Magellan Health Services, 2013). Difficulties arise in the form of medication side effects when systemically administered psychotropics are transported

via cerebral circulation, cross the blood-brain barrier, and in turn effect neuronal excitation and inhibition in areas of normal brain function (Labar & Dean, 2002).

In addition, most of these medications are prescribed off label (Bonati & Clavenna, 2005). It is estimated that currently more than 75% of the prescriptions written for psychiatric illness in this population is off label in usage (Magellan Health Services, 2013) and 96% of the off-label use was determined to have little or no sound scientific evidence for the condition for which the drug was prescribed (Edersheim, 2009). Difficulties of having few FDA approved psychotropic medications for children have been exacerbated by black box warnings placed by the FDA on antidepressants, and antipsychotics regarding their use in children and young adults (Edersheim, 2009) of potentially dangerous and life threatening side effects. In epidemiological studies regarding the rate of psychiatric medications prescribed to children and adolescents, the U.S has the highest prevalence of prescribing antidepressants and psychostimulants (Bonati & Clavenna, 2005).

Generally speaking, there are high rates of diagnostic co-morbidity in childhood, and few studies have addressed the treatment of children with multiple disorders or other complex presentations (American Psychological Association [APA], 2006). According to the American Academy of Child and Adolescent Psychiatry (AACAP, 2012), there is some evidence for the treatment efficacy of psychotherapeutic agents in children and adolescents for major depressive disorders, ADHD, OCD, separation anxiety disorder, social phobia, generalized anxiety disorder, mania, tic disorders, and aggression/impulse control as evidenced by autism and disruptive behavior disorders.

On the other hand, these studies have relatively short end points that are within a few years of drug exposure, not the years required to study drug effects that manifest in adulthood (Andersen & Navalta, 2011). Most of the evidence for efficacy is limited to acute symptomatic improvement, with only limited attention paid to functional outcomes, long-term durability, and safety of treatment (APA, 2006).

This brings up an additional overarching issue to be considered in pediatric psychopharmacology, which is the fact that most medications used with children are administered off label, which means that they are used to treat symptoms/conditions for which they were not granted FDA approval (NIMH, 2012). This means that the FDA does not limit the manner in which a physician may use an approved drug, and medications can be prescribed for any reason shown to be medically indicated for the welfare of the patient. Once a drug is approved for commercial use, a physician can lawfully prescribe a different dosage for a patient or may otherwise vary the conditions of use from what is approved in the package labeling without notifying the FDA or obtaining its approval (Sadock & Sadock, 2009).

Overall, there is a limited evidence base for efficacy of psychotropic medications in children (American Academy of Clinical Psyciatrists [AACP], 2012). Because very few psychotropic medications are tested on children, researched-based guidelines for medication dosages exist for very few psychotropic medications prescribed to children (Administration on Children, Youth and Families, 2012). Much of the published clinical trial findings applied to children and adolescents have been extrapolated from single-

agent versus placebo drug trials using adult patients while measuring acute and short-term outcomes (Magellan Health Services, 2013).

Anecdotally, the prescribing of multiple psychotropic medications in the pediatric population is on the increase, and little data exists to support advantageous efficacy for drug combinations used primarily to treat co-morbid conditions (AACAP, 2001; Zito, Safer & Valluri, 2007). Additionally, as seen with the diagnostic difficulties with RAD, the lack of diagnostic clarity can result in adding multiple medications in an attempt to treat difficult symptoms (AACP, 2012).

The bottom line concern is that results from adult studies being extrapolated to children is not necessarily appropriate because of developmental differences in pharmacokinetics (what the body does to the drug) and pharmacodynamics (what the drug does to the body) (Sadock & Sadock, 2009). Based on the lack of long-term studies on children and adolescents (AACAP, 2011), researchers are not exactly sure how these medications affect a child's growing body, but it is known that children and adolescents are more sensitive to the side effects of the medication (NIMH, 2012).

The manifestation of early insult, which may also include genetic polymorphisms, is also often not immediate (Anderson & Navalta, 2011). Although all psychiatric drugs have specific biochemical effects, over time other neurotransmitter systems react to the initial effects and broader changes begin to take place in the brain and in mental functioning (Breggin, 2011). This is in line with the neurodevelopmental evidence on the sensitive periods of brain development noted earlier in this chapter, resulting with concerns that psychotropic medications can adversely influence brain development

during sensitive periods of development and produce permanent alterations of the nervous system, resulting in potentially harmful delayed consequences (Magellan Health Services, 2013).

Brain Stimulation Modalities

This last section of the literature review will discuss whether Vagus Nerve Stimulation (VNS) might be theoretically safe, and possibly efficacious, for the treatment of individuals between the ages of 5-7 who have been diagnosed with RAD. A survey of the available literature, and empirical data on VNS will be discussed, along with the relevant brain areas that could potentially be modulated by VNS. In addition to VNS, other brain stimulation modalities have been considered, and rationales for their non-inclusion will also be briefly discussed.

VNS is the only brain stimulation modality being suggested as a potential intervention for RAD for children between the ages of 5-7 years. The predominant rationale being that there have already been a significant amount of controlled clinical studies and trials that have been conducted utilizing the VNS device within the infant and pediatric populations for the treatment of treatment refractory epilepsy. VNS has been successfully used in the pediatric epilepsy population in children as young as 1.4 years of age, through the pre-adolescent stage all the way up to 17 years of age (Yu, et al., 2014). Moreover, these studies have indicated that the use of VNS in the pediatric epileptic population is safe and effective, with transient, minor and tolerable side effects, if any at all (Morris III, et al., 2013; Awaad, et al. 2011).

Evidence for VNS use in epilepsy meets the standard for AACAP "Clinical Guidelines", the AACAP indicates that until further research is done it can only be considered an option for refractory psychiatric disorders (Leonard, 2005) in patients 18 and older. However, based on the safety and efficacy of VNS in the pediatric epileptic population for the treatment of epilepsy, in conjunction with the fairly consistent observed mood and anxiety improvements in this population being treated with VNS, and potential targeted brain regions that regulate mood and anxiety (Fitzgerald, 2011; Malhi, et al. 2006) VNS is being suggested in the RAD pediatric population.

While it is acknowledged that there is skepticism and stigma attached to brain stimulation techniques in general, and there is no evidence to date in regard to this type of intervention for RAD, it is this writer's hope to present the current available information and provide an argument for additional research into this area for this specific population.

Brain-Stimulation Modalities Initially Considered

Currently, at least 13 forms of brain stimulation techniques exist that are either under development or in evaluation for applications to treat neurological and psychiatric conditions (Jotterand & Giordano, 2011). A few brain stimulation modalities such as Electroconvulsive Therapy, Transcranial Magnetic Stimulation, Repetitive Transcranial Magnetic Stimulation, Deep Brain Stimulation, Magnetic Seizure Therapy and Vagus Nerve Stimulation have already shown effectiveness in reducing symptoms associated with specific psychiatric disorders such as obsessive compulsive disorder, post traumatic stress disorder, depression, anxiety and attention deficit hyperactivity disorder

(Novakovic, et al. 2011; Leonard, 2005; Beauregard & Levesque, 2006; Stuss, 2011; Van Oustem, 2011).

Currently, some of the aforementioned interventions are also being investigated, and/or are actively in clinical trials, for the clinical treatment of schizophrenia, schizoaffective disorder, autism, bipolar disorder, bulimia, post traumatic stress disorder, Alzheimer's disease, obesity, pain, traumatic brain injury and Tourette syndrome (U.S National Institute of Health, 2014a; U.S National Institute of Health, 2014b; Martinez, Jurdi, & Zboyan, 2007; Mohr-Rodriguez, Slavickova & Hanka, 2011; Novakovic, et al. 2011; Fitzgerald, 2011); however, because of limited studies, small sample sizes, and weak study designs, there is not enough data to conclude that these techniques would be effective for treating any of these conditions (United Health Care [UHC], 2014).

Initially, Transcranial Magnetic Stimulation (TMS), Repetitive Transcranial Magnetic Stimulation (rTMS), Deep Brain Stimulation (DBS), Magnetic Seizure Therapy (MST), Vagus Nerve Stimulation (VNS) and Electroconvulsive Therapy (ECT) were all being considered as possible interventions for RAD in the pediatric population (children 5-7 years of age). However, upon a critical review of all of the available literature on these modalities, the decision to entirely exclude TMS, rTMS, DBS & MST was made. Some of the reasons include the potential for severe and possible lasting side effects, increased level of surgical invasiveness, level of physical and emotional discomfort during administration, little or no studies of use in the pediatric or adolescent populations, significant stigma, irreversibility of brain lesions, and negligible understanding regarding

the potential biological targets of the intervention(s), or indiscriminate biological targeting rendering it not applicable to the underlying substrates of RAD.

ECT was a second runner up to VNS as being considered as a possibly efficacious brain stimulation technique for the treatment of RAD due to ECT's long history of effectiveness in the treatment of mood disorders (Fink, 2004); however the targeting is indiscriminate in comparison to VNS as a result of the induction of a seizure. On the other hand, seizure induction has been implicated with neuroendocrine changes as well as having an effect on neurogenesis and synaptic plasticity (Eitan & Lerer, 2006; Vaidya, Siuciak, Du & Duman, 1999; Tendolkar, et al. 2013), which could also be beneficial in the treatment of RAD. In a more recent study, ECT was found to activate the HPA-stress axis (Fosse & Read, 2013), which if a possibility, would be deleterious to those with RAD.

One of the primary reasons this author decided against considering ECT is because the use of ECT in the pediatric population is extremely small, and limited to a diminutive amount of case studies and anecdotal collections of patients (Shoirah & Hamoda, 2011). The majority of these reports have insufficient information about the diagnosis, characteristics of ECT treatment, and outcome. There are also no controlled studies and little information about the predictors of response in the pediatric population, including stimulus characteristics and optimal anesthetic (Walker & Rey, 1997; Lima, et., al, 2013), though the recommendations for the use of ECT in this age group are similar to those in adults (Bloch, Levcoitch, Bloch, Mendlovic & Ratzoni, 2001). The American Academy of Child & Adolescent Psychiatry (AACAP) supports the use of ECT in

adolescents with severe Axis I disorders, and only as a last resort; however, the policy parameter does not address the use of ECT in the pediatric population because of insufficient data and clinical experience (Leonard, 2005).

An equally crucial reason for not moving forward with suggesting ECT for the RAD population in the specified age range is because of the long withstanding stigma associated with this procedure in the adult population, nonetheless suggesting it in the pediatric population. Reports of misuse and inaccurate media portrayal contribute to fears, especially when the treatment involves children and adolescents (Bloch, Sobol, Levkovitz, Kron & Ratzoni, 2008). Generally, ECT remains one of the most controversial and poorly understood psychiatric treatment; some view it as painful, barbaric, dangerous and inhumane treatment that includes pain, being "shocked", and having one's memory wiped out (Smith, Vogler, Zarrouf, Sheaves & Jesse, 2009). In recent study investigating the public's attitude toward ECT by Lauber, Nordt, Falcato & Rossler (2005), 57% of respondents considered ECT to be a harmful treatment, and only 1.2% were in favor of ECT. Generally, there appears to be a uniform prejudice toward ECT that does not significantly vary between individual, demographic, or cultural contexts. Complicating this is the fact that mental health and medical professionals also have similar perspectives.

Overall, these opinions have been difficult to alter by proof of efficacy in adult studies and some adolescent studies, owing to the stigma attached to it, which compounds the stigma associated with psychiatric illness in general (Wilkinson & Daoud, 1998).

Essentially, the medical system cannot work independently from public opinion, which tends to be more critical than informed.

Other reasons for renouncing ECT include the level of perceived invasiveness and fear of the procedure itself. The spectrum of side effects of ECT ranges from mild and moderate to severe and non-transient. While there is mounting evidence that ECT in the young appears similar in safety and effectiveness to ECT in adults (Walker, Koster & Rey, 1999), it is difficult to compare due to obvious developmental differences. There is a limited amount of literature of the side effects on the pediatric population, making it difficult to ascertain whether ECT affects a young person's brain adversely, as there have been no pre-post MRI studies in young patients and no reports on autopsies in persons who had ECT in their youth (Walter, Rey & Mitchell, 1999).

Adding to the complexities, there are contraindications for the use of ECT concomitantly with specific psychotropic medications. For example, the combination of lithium and ECT enhances anesthesia risks, the risk of prolonged seizures, and cognitive disturbances, and the combination of MAOI's and ECT enhance the risk of potential lethal complications (Baghai & Moller, 2008). Furthermore, the American Psychiatric Task force on ECT discourages combination antidepressant treatment in general due to the concern of increased adverse effects (Haskett & Loo, 2010).

Vagus Nerve Stimulation

VNS was approved for pharmacoresistant epilepsy in Europe in 1994 and in the U.S in 1997 (O'Reardon, Cristancho & Peshek, 2006). As of 1999, the FDA approved VNS as an adjunctive therapy for reducing the frequency of seizures in patients older

than 12 years, and a subcommittee of the American Association of Neurology also concluded that VNS is indicated for patients over the age of 12, and deemed it "Safe and effective", based on a preponderance of evidence obtained from randomized clinical trials (Amar, Levy, Liu & Apuzzo, 2008).

At that time, evidence was insufficient to recommend VNS for epilepsy in young children; however, there are new reports of long-term efficacy and VNS use in pediatric epilepsy (Morris III, et al., 2013). As of 2006, more than 80,000 VNS have been implanted worldwide, with 30% of those patients being younger than age 18 at the time of the first implant (Awaad, et al. 2011).

The potential use of VNS in Psychiatry arose from the observation that patients treated with VNS for epilepsy occasionally experienced mood improvement and that VNS produced changes in brain activation in depression relevant brain regions (Fitzgerald, 2011). Additionally, it is also known that antiepileptic drugs such as carbamazepine, valproate and gabapentin have been shown to play a major role in the pharmacologic treatment of mood disorders (Milby, Halpern & Baltuch, 2008), and neurochemical studies in both animals and humans revealed that VNS alters concentrations of monoamines within the CNS (George, et al. 2003). This information led to a pilot prospective study of VNS effects on mood in epilepsy patients, treated with either VNS device or anti –epileptic drugs. Significant mood improvement was found in the VNS group at 3 months, which appeared to be independent of any improvement in seizure control, suggesting that VNS was having a separate and distinct effect on

depressive symptoms. The same finding was independently reported in a European study at about the same time with a group of epilepsy patients (O'Reardon, et al. 2006).

Since the 1999 American Association of Neurology assessment of VNS, the FDA approved VNS for the adjunctive long-term treatment of chronic or recurrent depression in patients older than 18 years with a major depressive episode or recurrent depression, either unipolar or bipolar, not adequately relieved by 4 or more antidepressant treatments (Morris III, et al., 2013), and patients are not required to have failed ECT to be eligible for VNS (Marangell, et al. 2007). While evidence for VNS use in epilepsy meets the standard for American Academy of Child and Adolescent Psychiatry "Clinical Guidelines", the AACAP indicates that until further research is done it can only be considered an option for refractory psychiatric disorders (Leonard, 2005). The American Psychological Association takes a similar stance to both the American Academy of Clinical Psychiatrists and the FDA on this topic (UHC, 2014).

VNS has been, and still is, the first regulatory approved implanted device for the treatment of a psychiatric disorder; however, the use of VNS in children and adolescents with any Axis I disorders has not yet been studied or approved (Marangell, et al. 2007) by any association.

Informed Consent

As per the American Association of Neurology standards in regard to VNS for children 12 and over with intractable epilepsy, the patient must provide written informed consent, or legal guardian must give written permission and the minor provide written assent (U.S National Institute of Health, 2014a). There have been no parameters located

in regard to VNS for individuals younger than 18 for VNS, most likely due to the fact that VNS is not currently under consideration for neither psychiatric disorders nor epilepsy in children under 18 years of age.

On the other hand, there have been ten studies located, including 1 randomized controlled trial, where VNS has been used in children with intractable epilepsy within the age ranges of 1.4 years of age, through the pre-adolescent stage all the way up to 17 years of age (Yu, et al., 2014; Tanganelli, Ferrero, Colotto & Regesta, 2002; Rossignol, et al. 2009; Rychlicki, et al. 2006; Alexopoulos, et al. 2006; Klinkenberg, 2012; Benifla, Rutka, Logan & Donner, 2006; Elliott, et al. 2011; Majkowska-Zwolinska, Zwolinski, Roszkowski & Drabik, 2012; Colicchio, et al. 2010).

Upon a review of these studies, the informed consent process and procedures are scantly mentioned in some, while others have no mention of informed consent, Ethics Review Committees or Institutional Review Boards (IRB).

In studies by Rossignol, et al (2009), Sherman, et al (2008), Pastrana, et al. (2011), Elliott, et al (2011) & Rychlicki, et al (2006), procedures or issues pertaining to informed consent were not mentioned.

In the study by Majoie, et al. (2010), the authors note that written informed consent of parents was obtained.

In the study by Alexopoulous, et al (2006), the authors note that their study was approved by the Institutional Review Board, and in the study by Tanganelli, (2002), it was also noted that their study was approved by the local ethics committee and carried out in accordance to the provisions of the 1975 Declaration of Helsinki, which is a code

of ethic emanating from the Nuremberg Code of 1947 (Jotterand, McClintock, Alexander & Husain, 2010).

In the randomized controlled trial by Klinkenberg, et al (2012), the authors noted that all parents, guardians, and participants aged 12 years or above gave written and signed informed consent, and the ethics committee of their named hospital affiliation approved all procedures. Similarly, in a study by Hallbook, et al (2005), the authors noted that written informed consent was obtained; however, it was not noted by whom the informed consent was obtained by, the guardians or the child or both. They also noted that the ethics committee of their named hospital affiliation approved all procedures.

To make a comparison, the American Academy of Child and Adolescent Psychiatry (2004), devised a practice parameter for the use of ECT in adolescents, and within that parameter are informed consent guidelines. The guidelines note that every attempt must be made to educate the adolescent and parents regarding the procedure and its risks and benefits; written informed consent for ECT must be obtained from a parent, and the consent or assent of the adolescent should be obtained; the adolescents ability to consent or assent are dependent on his or her cognitive maturity and the severity of psychiatric symptoms; and, a second opinion should be obtained from an independent psychiatrist. The provision also notes that some states specify a mandatory minimal waiting period (usually 72 hours) between signing the consent document and commencing treatment.

VNS Method

VNS implantation is an outpatient procedure under local anesthesia, where a neurosurgeon makes two small incisions, and wraps unidirectional wire around the vagus nerve. This wire is then connected to a subcutaneous battery operated generator through a commercial device, the NeuroCybernetic Prosthesis (NCP), which is a multi-programmable, bipolar pulse generator about the size of a pocket watch. The device is implanted subcutaneously in the left chest wall through an 8 cm incision inferior to the midpoint of the clavicle (Milby, et al. 2008), which intermittently sends an electrical current through the wire and thus through the nerve that then conveys a signal through neural impulses into the brainstem. The device is turned on after the recovery post-implantation period, in most cases after 2 weeks (Mohr, Rodriguez, Slavickova & Hanka, 2011; George & Aston-Jones, 2010). It is important to clarify that no portions of the device, including the wire, are in the brain.

Clinicians following the patient control the frequency and intensity of the stimulation, and adjustments to the stimulation parameters are transmitted non-invasively from a computer or laptop to the VNS device by a handheld infrared wand placed over the device (Mohr, et al. 2011). Programming visits to review VNS settings take approximately 30 minutes (O'Reardon, et al. 2006) in an office setting. Adjustable parameters include pulse width, signal frequency, output current, signal on time, and signal off time. Typically, pulses are delivered to the vagus nerve 24 hours a day, or until turned off (Marangell, et al. 2007). Evidence from both clinical and neuroimaging studies of VNS suggest that the therapeutic brain effects are gradual over several months

(Conway, et al. 2012), with full benefit is observed after 6-12 months of stimulation, with sustained efficacy up to 2 years (Mohr, et al. 2011).

VNS programming parameters have been established and approved for both epilepsy and depression and have been found to be effective in double-blind, controlled studies, although there are slight variations across studies, and parameters may vary considerably in practice. The typical values for VNS therapy are a current between 1and 2mA, a rate between 20 and 30 Hz, a pulse width of 250-500 μs, and a duty cycle of 10% (signal on time of 30 seconds and a signal off time at 5 minutes) (Albert, Cook, Prato & Thomas, 2009; Milby, et al. 2008).

In the event a failure of an extended trial of VNS to be of therapeutic benefit, a patient may elect to have the device switched off and the implant left in place, or to have the pulse generator explanted leaving the stimulus electrode in situ. The electrode is left in situ because of concerns that the adhesions around the vagus nerve itself might increase the risk of injury during the removal of the electrode (O'Reardon, et al. 2006).

Safety, Tolerability and Special Precautions of VNS

The adverse effects of VNS are those associated with the procedure of implantation and those that occur as a consequence of stimulation.

The NCP device used in VNS has been successfully used in the pediatric epilepsy population in children as young as 1.4 years of age, through the pre-adolescent stage all the way up to 17 years of age, with adverse events similar to those in adults, as seen in the following 10 independent studies by (Yu, et al., 2014; Tanganelli, Ferrero, Colotto, & Regesta, 2002; Rossignol, et al. 2009; Rychlicki, et al. 2006; Alexopoulos, Kotagal,

Loddenkemper, Hammel & Bingaman, 2006; Klinkenberg, 2012; Benifla, et al. 2006; Elliott, et al. 2011; Majkowska-Zwolinska, et al. 2012; Colicchio, et al. 2010). Moreover, all of these noted studies have indicated that VNS therapy is a safe and effective treatment for drug-resistant epilepsy in children and adolescents, with little to no side effects.

The most common side effects resulting from device stimulation of the vagus nerve are voice alteration (55%), increased cough (24%), dyspnea (shortness of breath) (19%), neck pain (16%), dysphagia (13%), larygnismus (11%), and paresthesia (10%) (Marangell, Martinez, Jurdi & Zboyan, 2007). The majority of these side effects are transient and are described by most patients as a moderate inconvenience (Malhi & Sachdev, 2007). Rarely does vocal cord paresis persist after surgery (<1 in 1000), and usually resolves slowly over the ensuing weeks. These side effects can be minimized or reversible with reduction in the stimulation parameters, and most side effects decrease with time (George & Ashton-Jones, 2010).

As a safety feature, the NCP system is designed to shut off in the presence of a constant magnetic field, and therefore, each patient is given a magnet that when held over the pulse generator, turns off stimulation. When the magnet is removed, normal programmed stimulation resumes. This allows patients to control and temporarily eliminate stimulation-related effects during key behaviors like public speaking (voice tremor) or heavy exercising (mild shortness of breath) (George, et al. 2003). Interrupting stimulation in this manner does not interfere with pre-programmed stimulation (Malhi & Sachdev, 2002).

Adverse effects associated with the procedure of implantation are wound infections; however, they are infrequent (3%), and managed with antibiotics (George & Ashton-Jones, 2010). Some uncommon complications in the immediate postoperative period include fluid accumulation in the generator pocket, partial left sided facial paralysis, and Horner's Syndrome (Milby, et al. 2008).

Given the known efferent VNS effects, no cardiac events have been reported when the device is turned on for the first time after surgery (Milby, et al. 2008). VNS has not been shown to adversely effect any aspect of physiological function, including cardiac rhythm (as assessed by EKG and ambulatory Holter monitoring), pulmonary function or gastrointestinal motility and secretion. There is no evidence in favor of adverse cognitive or emotional effects of VNS (Boon, Moors, De Herdt & Vonck, 2006; Amar, et al. 2008; Al-Harbi & Qureshi, 2012). Conversely, the use of VNS has been linked to improvements in verbal recognition and enhanced working memory (George & Aston-Jones, 2010).

There appears to be no tolerance to VNS. The patient with the longest exposure to VNS has had the system operating for 17 years (George & Aston-Jones, 2010).
Due to its non-systemic nature, VNS can be combined with virtually all existing treatments for affective disorders, and has been combined safely with a wide range of medications including MAOI antidepressants (O'Reardon, Cristancho & Pesheck, 2006).

Contraindications of VNS therapy include having a history of bilateral or left cervical vagotomy and receiving diathermy (Marangell, et al. 2007). MRI's of the spine and joints are prohibited due to the nature of the implant and a computerized tomography

(CT) scan would need to substitute for a magnetic resonance imaging scan (MRI). Cell phones, microwave ovens, and airport security systems should not have any adverse effects on the functioning of the VNS device (O'Reardon, et al. 2006).

Putative Mechanisms of Action of VNS

Currently, the mechanisms of action of VNS remain unclear (Amar, et al. 2008) (Albert, Cook & Thomas, 2009; Nahas, et al. 2007; Milby, et al. 2008); however, based on supporting neuroimaging and neurochemical studies, there are a few theories regarding the putative mechanisms of action of VNS.

Supporting Studies

The vagus nerve is a parasympathetic efferent nerve that relays information to many areas of the brain (Sadock & Sadock, 2007), and originates from four nuclei in the medulla oblongata; the dorsal nucleus, nucleus ambiguous, nucleus of tractus solitarius, and spinal nucleus of trigeminal nerve (Ogbonnaya & Kaliaperumal, 2013). Through these routes, it is postulated that the nucleus of tractus solitarius sends direct projections to the amygdala and hypothalamus, through the pons and raphe (the primary serotnin containing areas of the brain) and other projections are made to the locus coeruleus (the primary norepinephrine containing area of the brain), which also connects with various forebrain structures including the obitofrontal cortex and prefrontal cortex (George, et al. 2003; Conway, et al. 2012).

VNS has the ability to excite or inhibit neuronal activity, thus affecting the neurotransmitter concentration in different regions of the brain (Albert, et al. 2009). VNS exploits the fact that cranial nerves are direct extensions of the brain because of the

reciprocal influences on the limbic system and higher cortical activity. The vagus nerve is predominantly an afferent nerve, and it is postulated that though these projections and connections, the necessary channels are provided by which VNS exerts its central effects (Malhi & Sachdev, 2002).

Several functional neuroimaging studies on depression via Positron Emission Tomography (PET), Single Photon Emission Computed Tomography (SPECT), Functional Magnetic Resonance Imaging (fMRI) and FDG PET (Fluorodeoxyglucose positron emission tomography) have been conducted in attempts to reveal the location and level of the brain's immediate response to VNS.

Regional cerebral blood flow (rCBF) has also been found to be decreased in the amygdala (Zobel, et al. 2005; Van Laere, Vonck, Boon, Versijpt, & Dierckx, 2014). Additional neuroimaging studies have also implicated the brain areas of the hippocampus, thalamus, cerebellum, left and right orbitofrontal cortex, limbic system, hypothalamus, medulla, brainstem, striatum, insular cortices, dorsolateral/ventrolateral prefrontal cortex, the right anterior dorsal cingulate, in conjunction with the amygdala and hippocampus as being affected by VNS (Chae, et al. 2003; Conway, et al. 2012; Albert, et al. 2009; Kosel, Brockmann, Frick, Zobel, & Schlaepfer, 2011; Narayanan, et al. 2002). Besides implicating the regions of the limbic system, here have been some variations across studies regarding the other brain areas implicated. Potential reasons for the variations across studies are due to small and heterogeneous patient populations with limited characterization of pre-stimulus conditions (Van Laere, et al. 2014).

In addition to neuroimaging studies, neurochemical studies in both animals and humans have revealed that VNS alters concentrations of gamma-aminobutyric acid (GABA), norepinephrine and serotonin within the central nervous system (George, et al. 2003; Mohr, et al. 2011).

Hypotheses Related to VNS Effects

One hypothesis as to the mechanism of action of VNS is that it induces changes in the neurotransmitters implicated in the pathophysiology of both anxiety and depression, which results in both mood and anxiety regulation. Current depressive models hypothesize dysregulation of interconnected brain structures in the frontal and limbic circuitry, and primary regions in this network include the prefrontal, cingulated and insular corticies, amygdala, hippocampus, striatum, dorsal thalamus, hypothalamus, and brainstem nuclei (Price & Drevets, 2010), of which most have been implicated in the documented neuroimaging studies.

Norepinephrine has long been considered to be a critical neurotransmitter system involved in the pathogenesis and regulation of anxiety, as its main actions are on the sympathetic nervous system (Sadock & Sadock, 2007) regulating the fight or flight mechanism. As a result, one theory is that VNS may have a blunting effect in the atypical responses to threatening or fearful stimuli in those who have experienced pervasive early life stress (Ogbonnaya & Kaliaperumal, 2013) because of VNS's direct stimulation of the norepinephrine control site. Similarly in regard to modulation of mood, because VNS upregulates norepinephrine and serotonin (Amar, et al. 2008), the result is a decrease of mood liability.

There is also evidence that VNS changes the metabolic activity of structures in the limbic system that are similar to changes seen with antidepressant treatment, which contribute to the same (Klinkenberg, et al. 2012; Marangell, et al. 2007; George & Aston-Jones, 2010; Milby, et al. 2008).

Additionally, BDNF has been found to modulate mood, regulate neuronal survival, development and plasticity, and in studies of both acute and chronic VNS in rats has been found to increase the expression of BDNF (Furmaga, Carreno & Frazer, 2012; Albert, et al. 2009; Mohr, et al. 2011). On the other hand, studies in the human population are limited to only one located (Lang, Bajbouj, Galliant, & Hellweg, 2006). It is also postulated that VNS promotes neurogenesis by ramping up the activity in the monoamine neurotransmitter producing sites, as a decrease in these neurotransmitters in animal studies has shown to inhibit neurogenesis (Ogbonnaya & Kaliaperumal, 2013).

Lastly, the vagus nerve and anxiety have been linked in the James-Lange theory of emotions, which is one of the oldest theories about the brain's origins of fear. This theory proposes that all emotions lie within the body, and that the brain interprets emotional signals through the vagus nerve, and through this mechanism, anxiety is experienced. This theory posits that the physiological experience of anxiety, such as shortness of breath and increased heart rate, results in the emotional experience of anxiety (Mandler, 1990). It has been theorized for many decades that the information channeling through the vagus nerve to the brain is an important part of anxiety regulation, and if vagus nerve stimulation may be able to directly affect that channeling process, this may be a powerful way of modulating anxiety (George, et al. 2008).

Vagus Nerve Stimulation and Reactive Attachment Disorder

While it is recognized that VNS is not approved for use in any other populations or age groups beside those noted earlier, the proposed mechanism of action of VNS appears to have applicability to the underlying substrates of RAD.

From a neuropsychological perspective, RAD is associated with early life stress, and early life stress is associated with abnormalities in the morphology and functioning of the human brain (Twardosz & Lutzker, 2010), specifically the amygdala, hippocampus, prefrontal cortex and corpus callosum. Similarly, depression and anxiety are also associated with similar differences in morphology and/or functioning of the human brain, specifically in the amygdala (Tottenham, Hare & Quinn, et al. 2010), hippocampus (MacMillan, et al. 2003), and prefrontal cortex (Rot, Mathew & Charney, 2009).

Depression, anxiety and early life stress associated with RAD all have in common similar the serotonin and norepinephrine neurotransmitter systems underlying the pathogenesis of these disorders (Ressler & Nemeroff, 2000; Joels & Baram, 2009; Frigerio, et al. 2009). VNS has been found to alter concentrations of serotonin and norepinephrine within the CNS (George, et al. 2003), and has direct projections into the limbic system structures (Amar, et al. 2008) implicated in the pathogenesis of depression, anxiety and RAD.

Supporting the potential application for the use of VNS in RAD are the studies with epileptic populations where VNS has had positive effects on mood and anxiety, strengthening the association between the mechanisms of VNS and its potential

applicability to the RAD population. Of similar importance to note is that the RAD population has already been being treated psychopharmacologically with mood stabilizers on an off-label basis.

Because VNS has the ability to excite or inhibit neuronal activity, which affects the neurotransmitter concentration in only the desired regions of the brain (Albert, et al. 2009), it is postulated that VNS may be more effective, and have less side effects, than current psychopharmacological treatments currently in use for RAD. Adding to the rationale for the use of VNS with the RAD population is that only the specific, desired brain region will be targeted, and the modulation in neurotransmitters will only occur in the area requiring it, which will result in limited undesired side effects, and more focalized treatment. Behind the mechanism of action of psychopharmacological treatments, difficulties arise in the form of medication side effects when systemically administered psychotropics are transported via cerebral circulation, cross the blood-brain barrier, and in turn effect neuronal excitation and inhibition in areas of normal brain function (Labar & Dean, 2002).

The ultimate goal in suggesting VNS be utilized in the RAD population is not only due to the suggested limited side effects and increase in focalized treatment, but because the limited amount of office visits and diminutive length of treatment time in comparison to traditional psychiatric treatments (O'Reardon, et al. 2006), the minimum level of invasiveness in comparison to alternative brain stimulation techniques (Malhi & Sachdev, 2007), and the established safety and tolerability of VNS in the epileptic pediatric populations (Morris III, et al., 2013; Awaad, et al. 2011; Yu, et al., 2014).

Additionally, VNS would allow researchers and clinicians to elucidate its mechanisms in a cost-effective manner in comparison to the treatments currently in place (Sperling, Reulbach & Kornhuber, 2009; Krahl, Senanavake, Pekary & Sattin, 2003).

CHAPTER 3. REVIEW OF SUPPORTING EVIDENTIAL STUDIES

The purpose of this chapter is to compose a critical review of the quality of the research on VNS that is included in the literature review as supporting evidence for the potential use of VNS in children ages 5-7 years of age with RAD.

Clinical Outcomes of VNS on Mood in Patients with Epilepsy

To date, the main use of VNS has been to reduce seizure frequency in both adults and children and with treatment-resistant epilepsy. Anecdotal reports of mood improvements in VNS implanted epilepsy patients suggested that VNS might be helpful in patients with depression and anxiety, and functional imaging studies supported this idea as VNS was found to increase activity in several brain regions thought to be involved in the pathogenesis of these psychiatric conditions (Malhi, et al. 2006). Studies of mood improvements secondary to the use of VNS in both the adult and pediatric epilepsy populations have had promising results and support the suggestion that VNS may be effective in the RAD population due to similarities in the pathogenesis of these disorders.

Two randomized clinical trial (RCT) studies showed significant improvements in standard patient-reported mood assessment scales in adult patients with epilepsy when results before implantation were compared with results post-implantation.

One study by Elger, Hoppe, Falkai, Rush & Elger (2000) evaluated 11 subjects 1 week pre-implantation (baseline) and 3 and 6 months post-implantation. Before VNS therapy, 7 of the 11 patients met criteria for sub-depressive mood by the Montgomery-Asberg Depression Rating Scale, and the group's mean was within the sub-depressive

mood range; the mean after VNS was in the non-depressed range. Scores improved at the study's 3-month follow up ($p<0.05$), and mood improvements were sustained in 9 of 11 patients at the 6-month follow up.

In a second study by Harden, et al. (2000), 20 adult subjects were evaluated 3 months pre and post VNS implantation using the clinician administered Cornell Dysthymia Rating Scale (CDRS) and Hamilton Depression Index (HAM-D), as well as the patient self-report Beck Depression Index (BDI). Improvements in mood were found in all three scales (CDRS $p=0.001$, BDI $p=0.045$, HAM-D $p=0.017$). The group's mean BDI score pre-VNS treatment was 12.0 (mild mood disturbance); this decreased to 9.4 (non-depressed), post-VNS therapy. Further, BDI scores significantly decreased relative to those for the epilepsy control group who received no VNS treatment, studied over the same period ($p=0.01$). The benefit was not correlated with reduced seizure frequency or with stimulation frequency or intensity.

Two open clinical cohort studies also had similar results to the RCT studies, as one of the studies with the adult epileptic population showed significant improvements on standard patient-reported mood assessment scales and the other study with the pediatric epileptic population showed improvements, albeit not significant.

In one open clinical cohort study by Klinkenberg, et al. (2012), 41 adult patients with refractory epilepsy were treated with VNS as a part of usual patient care. A neuropsychological battery was performed during baseline and repeated after 6 months of VNS in order to compare neuropsychological variables before and after VNS. Three variables were evaluated: mood, cognition and quality of life; mood was assessed by the

Profile of Mood States (POMS), global cognition was assessed with the Raven Standard Progressive Matrices, and quality of life was assessed by the Quality of Life in Epilepsy Inventory questionnaire (QOLIE-89), which assesses the patients rating of their memory, level of physical and mental well-being, energy, depression, worries about seizures and work, social limitations, and overall quality of life. Significant improvements were observed for both mood and quality of life after 6 months of VNS; based on the results of the POMS and QOLIE-89 questionnaires ($p<0.05$). Additionally, the four subscales of the POMS showed significant improvements in anxiety, and mood improvements of the patients were correlated with a significant increase in QOL, confirming the opinion of the researchers that the opinion of mood disturbance would be the most important variable that affects the QOL of patients. There was no significant change in cognition and no significant correlation was found between changes in seizure frequency and improvements in mood or quality of life.

In a second open clinical study by Hallbook, et al. (2005), 15 children aged 4-17 years with refractory epilepsy were treated with VNS initially, and after 3 and 9 months of VNS treatment. Three variables were evaluated: mood, cognition and quality of life. These variables were evaluated through use of the following instruments: Bayley Scales of Infant Development (BSID), Wechsler Preschool and Primary Scale of Intelligence (WPPSI-R), Wechsler Intelligence Scale for Children (WISC-III) depending on the child's level of functioning, a Visual Analogue Scale for validating quality of life, Child Behavior Checklist (CBCL) for quantifying behavioral problems, the Dodrill Mood Analogue Scale and the Birleson Depression Self-Rating Scale. There was improvement

in the depressive, mood and quality of life scales; however, results were not significant; 5 of 15 children showed improvements in depressive parameters, and 12 of 15 showed improvement in quality of life. There were no changes in cognitive functioning.

Limitations of VNS on Mood Studies in Epileptic Populations

While there are have been 2 RCT's that had the same significant results, and this data indicates that VNS is possibly effective for mood improvements in patients with epilepsy, the lack of studies is notable. VNS dosing effects appear to be inconsistent across studies, contributing to difficulty in comparing results and effects. Additionally, there are several confounding variables including other treatments being used concomitantly with VNS therapy. Different clinical measures were used in between studies, making it difficult to make correlations between studies.

Clinical Outcomes of VNS on Quality of Life (QOL) in Patients with Epilepsy

In numerous studies conducted with the epileptic population, QOL was assessed to determine whether or not VNS had a positive effect in other facets of their life on top of, and independent of, decreases in seizures. Though QOL was assessed using different instruments, and the definition and quantification of QOL varied across the studies noted in the following section, it is understood that QOL refers to the overall reported well-being of an individual.

In the following studies pertaining to quality of life assessments in the epileptic populations receiving VNS, though some results did not meet statistical significance, QOL appeared to improve in the individuals participating in these studies. Though there are no studies correlating RAD with QOL, and there are no studies associating QOL with

specific neurobiological correlates, quality of life is inherently injured in those with RAD due to the complexities behind their mentalization and attachment representations (Mikic & Terradas, 2014).

The results of the proceeding studies support the previous noted studies where VNS resulted in improvements in both mood and anxiety, again supporting the suggestion that VNS may be effective in the RAD population due to similarities in the pathogenesis of these disorders.

Currently, there are no randomized controlled trials of QOL after VNS; however, there are open clinical studies and retrospective analyses of patient data obtained clinically (Sherman, et al. 2008). Three studies were located assessing the QOL outcome after VNS in both the pediatric and adult population with epilepsy, and though results were not all significant, improvements in QOL were reported.

In one open clinical study by Ergene, Behr & Shih, (2001) on 17 adult patients with epilepsy, the Quality of Life in Epilepsy-10 (QOLIE-10) questionnaire consisting of questions designed to assess the patient's rating of their memory, level of physical and mental well-being, energy, depression, worries about seizures and work, social limitations and overall quality of life on VNS treatment, was administered before and at 1-3 weeks, 5-7 weeks, 3 months, 6 months, and 9-12 months after the initiation of VNS. QOLIE-10 scores were significantly improved after the initiation of the therapy when compared to the baseline (p=0.01). Additionally, there was no correlation found between the QOLIE-10 scores and reduction in seizure frequency.

Significant results were also found in another open clinical study by McLachlan, et al. (2003) in the assessment of the QOL in patients with epilepsy. This study consisted of a total of 27 subjects, both children and adults (12-46 years of age), over the course of 12 months. Patients who were over the age of 16 and had no cognitive impairments were administered the Quality of Life in Epilepsy-10 (QOLIE-10), and the Epilepsy and Learning Disability Quality of Life (ELDQOL) measure was used for caregivers of children and those with mental impairment. Additionally, a subjective global rating of the patient's perception of treatment using a 7-point Likert scale was given at the end of the treatment year. The mean overall QOLIE-89 scores increased significantly from 60.9 preoperatively to 67.3 after 12 months of treatment for a mean change of 6.4 (p=<0.01), indicating a favorable effect of VNS. As with the other studies reported previously, there was no significant correlation found between the QOLIE-10 scores and reduction in seizure frequency.

In one study located by Sherman, et al. (2008), also investigating the QOL in patients with epilepsy, significant results were not found, though there were meaningful increases in QOL for the group who received VNS. This study included 34 children (3-18 years of age) who underwent VNS, and another 19 children in a second group who did not receive VNS, but medical management instead. The patients in the VNS group all had the most severe cases of epilepsy in this study's program. All patients had been diagnosed with chronic intractable epilepsy, and they were given a self-administered quality of life scale, the Impact of Childhood Neurologic Disability Scale (parent or self-report), which assesses the impact of epilepsy on the child and family according to four

scales: behavioral, cognitive, physical limitations and epilepsy. Results showed that a greater number of children in the VNS group had meaningful increases in QOL compared to the medically managed group who did not receive VNS (33% versus 11%); however, this difference did not reach statistical significance.

Limitations of VNS on QOL Studies in Epileptic Populations

Limitations to studies regarding the assessment of the QOL in the epileptic populations are difficult to compare due to the notably distinct differences in the measurements used, which most likely accounts for some of the differences in results between studies. Some of these measurements originate from different raters, such as self or parent, which also introduces potential for error because quality of life may differ in different settings and contexts and because of inherent rater biases that affect inter-rater reliability. Additionally, because some of these studies used different measurements to assess QOL, this introduces a high probability that each measurement does not assess qualities within the same domain(s).

Another limitation to the QOL studies is the absence of true control groups to determine whether improvements or declines in quality of life would have occurred with or without treatment as a result of other extraneous, uncontrolled variables. Sample sizes and age ranges in these studies are also different and vast, potentially contributing to the discrepant results. As noted earlier, there are no randomized controlled studies on quality of life in patients with epilepsy, and the studies noted were also not blinded, which places methodological constraints on the studies, and decreases the robustness of the results.

Nevertheless, these open clinical trials do provide empirical data, which has provided researchers with the preponderance that VNS may be efficacious in psychiatric disorders.

Adverse Effects of VNS in the Pediatric Population

Adverse effects of VNS were previously discussed in the literature review section; however, a critical review of the studies associated with VNS in the epileptic pediatric population is essential in formulating a coherent rationalization for the potential safety and tolerability in the pediatric RAD population.

To date, there are many less publications that address the effectiveness and safety of the VNS device in children as compared to adults (Alexopoulous, Kotagal, Loddenkemper, Hammel & Bingaman, 2006). As a result, publications that analyze the safety and tolerability of VNS on the pediatric population will be included in this section; tolerability and safety of VNS in adults was previously discussed. Results of this section indicate that children may have a greater risk for wound infection than adults due to behaviors more common in children, and extra vigilance in monitoring for occurrence of site infection in children should be undertaken.

A randomized controlled trial (RCT) by Klinkenberg & Aalbers, et al. (2012) studied 41 children, 23 males and 18 females; mean age at implantation 11 years, 2 months, SD=4 years, 2 months, age range of 3 years 10 months-17 years 8 months. The most frequently reported adverse effects were voice alteration (8 participants), coughing (3 participants), and throat pain (3 participants). The majority of side effects were transient (tingling sensation in the throat-2 participants, headache-1 participant, pain around stimulator during exercise-1 participant, itch-1 participant). Two patients had mild

infections and in these cases, there was no need for device removal and both infections were successfully treated with short-term antibiotics. There were no other surgery related effects. Discontinuation during the study because of side effects did not occur. The investigators of this RCT concluded that VNS is a safe and well tolerated treatment for children.

The authors Rossignol, et al. (2009) conducted a retrospective study of 28 children and adolescents, age range 3.5-21 years of age when VNS was initially initiated. VNS therapy was ongoing for 6 weeks. Side effects occurred in 68% of the patients, and most were mild and transient. Six patients experienced severe side effects including two infections requiring removal of the implant and antibiotic treatment, with subsequent re-implantation of VNS, and two severe discomforts at the site of the battery requiring surgical repositioning and two cases of severe dysphagia. In the cases where VNS was re-implanted, therapeutic effects were comparable following reimplantation as prior to removal. There was one death, unrelated to VNS, as the child was left unsupervised with solid food.

A retrospective analysis of 13 children who had intractable epilepsy was conducted by Pastrana, Estronza & Sousa, (2011). The mean age at implantation was 12 years (range 6-18, SD=5). Seventy-seven percent (77%) were female and 23% were male. In this study, one patient developed a wound infection that was successfully treated with IV antibiotics and cleansing and debridement.

A retrospective study by Alexopoulos, et al. (2006) was conducted to determine the long-term efficacy of VNS in children with pharmacoresistant epilepsy, and to

compare the efficacy in two age groups, pre-adolescent children <12 years of age at the time of VNS implantation, versus adolescent children >12 years of age. This study included 49 patients, and pre and post data were available for 46/49 patients. Median follow up was 2 years; follow up exceeded 4 years in 9/46 patients. Median age at implantation was 12.1 years (range 2.3-17.9 years, SD=4.3). Twenty-one patients (45.6%), 10 girls and 11 boys, were under 12 years of age at the time of surgery. The remaining 25 patients, 11 girls and 14 boys, had the device implanted between the ages of 12 and 18 years.

Among this cohort, 6 patients required replacement of the generators battery within 2.5-4 years after initial implantation. Five patients developed a wound infection around the device (within 1 week to 6 months after implantation). The rate of deep infections necessitating device removal was 7.7% (4 of 46 patients). One out of the 4 explanted generators was subsequently replaced. Three patients died during the period of observation: two of sudden unexpected death in epilepsy and the other following surgery unrelated to VNS.

> Several patients (56.5%) experienced stimulation induced symptoms (throat pain, hoarseness, cough, drooling) that did not require device removal. These symptoms were usually mild and transient, and only limited changes of the generator's stimulation settings in 3/46 patients (6.5%). There were no cases of lead fracture. There was no statistically significant difference (Wilcoxon rank-sum test) in the number of AED's at the time of implantation (on average 2AED's, ranging from 1-3 in the younger and 1-4 in the older group) or the

number of failed AED's prior to VNS therapy (which ranged from 4-12 in either group). (Alexopoulous, et al., 2006, pp 500)

A clinical trial by Zamponi, Petrelli, Passamonti, Moavero & Curatolo, (2010) studied 254 patients with refractory partial epilepsy (mean age 32 years, range 13-60). Surgical infection complications occurred in 3 patients; all were explanted and one was re-implanted later in the study.

Left vocal cord paralysis occurred in 2, lower facial muscle paresis occurred in 2, and fluid accumulation over the generator requiring aspiration occurred in 1. The frequency of adverse effects (AE's) was dose related (greater at the highest-tolerated stimulation intensity versus the lowest perceptible stimulation intensity: voice alteration 47.7% versus 9.7%, dyspnea 11.6% versus 1.0%, pharyngitis 15.8% versus 3.9%. Two additional patients discontinued the study due to AE's. When these adult data were used, infection risk at the VNS site in children (30/764) was increased relative to that in adults (3/254). The investigators of this RCT concluded that VNS is a safe and well tolerated treatment for children.

A study of 15 children with therapy resistant epilepsy was conducted by Hallbook, et al. (2005), to determine the impact of VNS on cognition, quality of life, behavior and mood. In this study, there were a total of 15 children, (10 boys and 5 girls) aged 4-17 years (median 11 years). In this study, no side effects were seen either from the surgical procedure of from VNS itself. Transient coughing and hoarseness for 1 or 2 days after increasing the current was reported in 4 patients. Weight loss was seen in 1 adolescent and one had non-transient pain and paresthesia in the neck that was so

disabling that quality of life behavior score and mood were affected and the stimulator was withdrawn after the study was finished. One child was complaining of shortness of breath that did not improve completely until the pulse width was reduced from 500 to 250 ms after 9 months.

The authors Elliott, et al. (2011) analyzed the efficacy and safety of VNS in 141 children 18 years of age and younger with treatment resistant epilepsy, and compared the safety and efficacy in children under 12 years with the outcomes in older children. The patients mean age at VNS implantation was 11.1 years (range 1-18 years). Eighty-six children (61%) were younger than 12 years at the time of VNS implantation, constituting off-label usage. Major (3) and minor (6) complications occurred in 9 patients (6.4%) and included 1 deep infection, 1 seroma/hematoma treated with aspiration, persistent cough in 1 patient, severe but transient neck pain in 1 patient, and hoarseness in 2 patients. There was no difference in efficacy or complications between children 12 years of age and older, and those younger than 12 years of age. The authors concluded that VNS is a safe and effective for treatment resistant epilepsy in young adults and children.

In a 2-year follow up by Majoie, Berfelo, Aldenkamp, Renier & Kessels (2010), the authors investigated the efficacy and safety of VNS in 19 children, age 5.9-18.8 years, mean age 10.8 years, with catastrophic childhood epilepsy. Side effects included coughing (n=4), and a strange feeling in the throat (n=2), which all resolved after the first week of stimulation. Hoarseness only occurred during the time the patient was stimulated and was present in 7 patients. This side effect persisted until the second month of

stimulation. One patient encountered swallowing difficulties and the device was deactivated during meals as a result. No surgical complications occurred.

In a study of 74 children (mean age 8.8 years, range 11 months-18 years) by Wheeler, et al. (2011), the efficacy of VNS was analyzed among the epileptic population. The minimum follow up for this study was 1 year and a mean follow up of 2.2 years. Four children (5.4%) had the device removed for non-efficacy and intolerance, including symptomatic tachycardia and fever of unknown origin (1 each) and discomfort at the site (2 patients). Infectious surgical complications occurred in 6 (7.1) including deep infection requiring explanation in 3 (3.6%) and superficial infection treated with oral antibiotics (2 patients) and with IV antibiotics and surgical debridement (1 patient). Two patients experienced electrode fracture and one had ipsilateral vocal cord paralysis. One patient each reported hoarseness, cough, involuntary arm movement, inappropriate laughter, drooling, torticollis, and urinary retention. One of the 2 electrode fractures was thought to result from the child pulling at the surgical site.

Clinical Outcomes of VNS in Patients With Mood Disorders- Reported to the FDA

In addition to previous studies on VNS in mood and epilepsy, the antidepressant efficacy of VNS has also been evaluated in patients with treatment resistant major depression.

Most of the available evidence regarding the safety and efficacy of VNS for depression comes from the studies funded by or preformed in collaboration with Cyberonics, Inc. Data from these studies were presented to the FDA to support the Premarket Approval Application. Overall, several studies were preformed, and

complete data sets have not yet been published for all of these studies. (UHC, 2014, pp 5)

Though results were mixed and the use of VNS in individuals with mood disorders were not all statistically significant, the following studies support the increase in quality of life reported by those with intractable epilepsy, and also provide additional support for the mood improvements reported by those with intractable epilepsy. As a result, the rationale for the use of VNS in the RAD population continues to be supported by these studies.

A 10-week acute, double blind, randomized controlled trial was conducted by Rush & Marangell, et al. (2005). Prior to the start of the acute 12-week phase of the study, 235 patients were implanted with the VNS therapy device; of these, 119 patients were randomly allocated to have the device activated at a specific dose and 116 patients were randomly allocated to the sham control arm in which the implanted device was not activated. After the acute phase was completed, the device was activated for these 116 patients.

All of the adult patients presented with treatment resistant non-psychotic depressive disorder, or non-psychotic depressed phase bipolar disorder, participants could be taking up to a total of 5 antidepressant, mood stabilizer, or other psychotropic medications, provided the medication type and dosage were kept stable throughout the baseline period. After the 2-week, single blind recovery period (no stimulation), 10 weeks of masked active or sham VNS followed implantation. Psychotropic medications were kept stable and no medication increases were permitted during the trial. Clinical

assessments of depressive symptoms included the Hamilton Rating Scale for Depression (HRSD), the self administered Montgomery-Asberg Depression Rating Scale (MADRS), and the Inventory of Depressive Symptomology (IDS-SR). To assess inter-rater reliability, the HRSD interviews were videotaped at key time points, including baseline and acute phase termination. The Clinical Global Severity (CGI-S) and Improvement (CGI-I) ratings were used to assess overall symptom severity and change. Functional outcomes for quality of life were assessed using the Medical Outcome Study Short Form -36 (MOS SF-36).

For the HRSD scores, the intra-class correlation coefficient (ICC, single rater) across the 379 interviews was .94, indicating high inter-rater reliability for the HRSD scores.

The difference in the HRSD response rates was not significant (chi square=1.32, *df*=1, *p*=.251); however, the difference in the IDS-SR response rates was statistically significant (chi square=4.62, *df*=1, *p*=0.32). Two other secondary measures of efficacy were not statistically significant, the MADRS (chi-square=.778, *df*=1, *p*=.378) and the CGI-I chi-square =.208, *df*=1, *p*=.648). A repeated measures linear aggression analysis was performed for the evaluable sample for raw scores of the active versus sham. At 12 weeks, the estimated difference for the HRSD was -.769, SE .80, 95% CI (-2.34, .80), *p*=.336 and the estimated difference for the IDS-SR was -2.374, SE 1.23, 95% CI (4.78, 0.3), *p*=0.53. The active and sham VNS groups did not differ on either physical or mental component of the MOS-SF36. For the physical component, mean change

was -.0 (SD=8.3) for the VNS group (n=107) and -1.6 (SD=8.4) for the sham group (n=107; F=.50, *df*= [1,208], *p*=.480, ANCOVA). For the mental component, mean change was 5.0 (SD=11.6) for the VNS group (n=107) and 4.0 (SD=10.2) for the sham group (n=107; F=.69, *df*=[1, 208], *p*=.406, ANCOVA). Results indicated that the study did not yield definitive evidence of short-term efficacy for adjunctive VNS in treatment-resistant depression. (Rush & Marangell, et al, 2005, pp. 351)

This 10-week acute phase was followed by an uncontrolled, naturalistic long-term study by the same authors, to determine whether statistically significant or clinically meaningful symptom reductions occur with VNS over the longer term, and to examine the long-term tolerability and safety of VNS. Participants included in the analysis of the 12-month study had been previously randomized to either active or sham during the 10-week acute phase. The participants in the initial active group received another 9 months of VNS, while those in the initial sham group received 12 months of VNS. Individuals who initially received the sham VNS had to re-qualify to be included in the 12-month analysis, which required having 2 HRSD assessments after 8 and 10 weeks of sham VNS to establish baseline before activation of the VNS device. Those who initially received active VNS in the randomized acute trial who continued in the study had to have at least one HRSD assessment after completing the acute phase. The protocol allowed changes in the in the types and doses of any psychotropic or other medications after the 10 weeks of active VNS for both groups. In addition, other somatic treatments such as ECT and rTMS were allowed, as was the addition or deletion of psychotherapy,

The primary outcome measure was change over time in the scores of the HSRD. Secondary outcome measures included the Montgomery Asberg Depression Rating Scale (MADRS), the Clinical Global Impression Scale (Severity-CGI-S and Improvement-CGI-I) subscales. For those who initially received sham VNS, a new baseline was established by averaging these ratings obtained after 8 and 10 weeks of sham VNS. For this group, ratings for the clinical assessments were obtained just before VNS activation, and after 1, 2, 3, 4, 6, 8 and 10 weeks of the VNS. The CGI-I was collected just before initiating active VNS for the sham group, and after 10 weeks of VNS. After 10 weeks of active VNS had been delivered to each participant, assessments were obtained monthly. The primary analysis revealed a significant reduction in the HRSD scores (average improvement was .45 points per month, p=<.001). At exit, HRSD revealed that 27.2% of evaluable participants achieved a response at exit, and 158% achieved a remission. Similar results were obtained with the MADRS: 28.2% response and 20.3% remission. Furthermore, most (73.1%) of those with a response by HSRD during the final quarter of stimulation met the researcher's a-priori definition of a "Sustained HSRD response".

There was a general pattern of increasing response rates observed at 3, 6, 9, and 12 months based on the assessments, and a statistically significant increase in response rates was seen between 3 and 12 months for HRSD and MADRS (p=<.005), (Rush & Sackeim, et al. 2005).

The above studies by Rush & Marangell, et al. (2005) and Rush & Sackeim, et al. (2005), were flawed by the concomitant use of antidepressants and adjusted treatments of both the VNS and drugs during the study period. There was also a lack of a comparative

group. Additionally, a financial relationship with the manufacturer limits the validity of the results. The researchers Martin & Sanchez (2012) conducted a systematic review and meta- analysis of analytical studies to determine the efficacy of VNS for the treatment of depression. Fourteen studies met the selection criteria and were included in the review. The meta-analysis of efficacy for uncontrolled studies showed a significant reduction in scores of the HDRS and the percentage of responders having been at 31.8%. However, the above RCT by Rush & Marangell, et al. (2005) which reported no statistically significant differences between the active intervention and the placebo groups, was of interest. To study the cause of this heterogeneity, a meta-regression was preformed. The adjusted co-efficient of determination was 0.84, which implies that an 84% variation in effect size across studies was explained by baseline severity of depression.

In a multicenter open non-randomized, uncontrolled trial by Rush & George, et al. (2000), of 30 adult outpatients (18-70 years of age) who had failed at least two robust medication trials in the current major depressive episode while on stable medication regimens completed a baseline period followed by VNS implantation. A 2-week single blind recovery period (no stimulation) was followed by 10 weeks of VNS. Efficacy and safety data were gathered at two baseline visits at weeks 1 and 2, and weekly for 10 more weeks after implantation. Clinical assessments of depressive symptoms included the Hamilton Depression Rating Scale (HDRS), and the Montgomery-Asberg Depression Rating Scale (MADRS). The Clinical Global Impressions-Improvement Index (CGCI-I) gauged the overall status and responses. Response rates (>50% reduction in baseline scores) were 40% for both the HDRS and the Clinical Global Impressions-Improvement

Index, and 50% for the Montgomery-Asberg Depression Rating Scale. Symptomatic responses, accompanied by substantial functional improvement, have been sustained during the long-term follow up of 4-9 months. No patient received concomitant ECT, investigational drugs, or treatment with another investigational device during the study, and no patients discontinued VNS due to adverse side effects.

There was an open, naturalistic follow up study conducted by Marangell, et al. (2002), which studied the effectiveness of 12 months of VNS therapy in the 30 patients that were enrolled in the above study by Rush, et al. (2000). Twelve of the patients had greater than or equal to 50% improvement on the HDRS and 15 showed the same level of improvement on the MADRS. Approximately 29% of the patients achieved remission in this timeframe.

The limitations of the above studies by Rush & George, et al. (2000) and Marangell, et al. (2002), include small sample size, lack of statistical power analysis, and small sample size. The validity of the results are also limited due to the financial relationship with the manufacturer.

The results of another long term follow up study by Nahas, et al. (2005) showed long-term benefits associated with VNS in those with major depression. In a two year, open, acute phase pilot study, 59 outpatient participants with treatment resistant major depressive episodes were examined in regard to the effects of adjunctive VNS. Changes in psychotropic medications and VNS stimulus parameters were allowed only after the first 3 months. Clinical assessments of depressive symptoms included the Hamilton Rating Scale for Depression (HAM-D-28). Response was defined as > or 50% reduction

from the baseline HAM-D-28 total score, and remission was defined as a HAM-D-28 score < or=10. HAM-D-28 response rates were 31% (18/59) after 3 months, 44% (26/59) after 1 year, and 42% (25/59) after 2 years of adjunctive VNS. Remission rates were 15% (9/59) at 3 months, 27% (16/59) at 1 year, and 22% (13/59) at 2 years. These results suggest that patients with chronic or recurrent treatment resistant depression may show long-term benefit when treated with VNS. The lack of a control group, the concurrent medication therapy and financial relationship with the manufacturer limits the validity of the results of this study.

An open, uncontrolled European multi-center 12-month study conducted by Schlaepfer, et al. (2008) included 74 patients with treatment-resistant depression. Baseline depression severity was compared to ratings 2 weeks after implantation, after 3 months of VNS and after an additional 3, 6, and 9 months. Response was defined as a >50% reduction in the Hamilton Depression Rating Scale (HAMD-28). Secondary outcomes were assessed on the Montgomery-Asbery Depression Rating Scale (MADRS) and the Inventory of Depressive Symptomology Self-Rated (IDS-SR). After 3 months of VNS, response rates reached 37% and remission rates reached 33%. Response was denied as sustained if no relapse occurred during the first year of VNS after response onset; 44% of patients met this criteria. There was no comparison group for this study, so response with a different treatment or no treatment remains unknown. Additionally, patients were not blinded, and they had regular clinic visits, both of which could affect responses to a subjective outcome measure.

The researchers George, et al. (2005) completed a one-year comparison of 205 patients with VNS and treatment as usual (TAU). The two groups had similar baseline demographic data, psychiatric and treatment histories, and degrees of treatment resistance, except that more TAU participants had at least 10 prior major depressive episodes, and the VNS+TAU group had more ECT before study entry. VNS +TAU was associated with greater improvement per month in the Inventory of Depressive Symptomology scale (IDS-SR) than TAU across 12 months (p=<.001). Response rates according to the Hamilton Rating Scale for Depression (HRSD) at 12 months were 27% for VNS+TAU and 13% for TAU (p=<.011). Both groups received similar TAU (drugs and ECT) during follow up. This study was flawed by the lack of randomization, including the fact that all principal investigators disclosed a financial relationship with the manufacturer.

In a study by Nierenberg, et al. (2008), the authors described the outcome of VNS for bipolar treatment -resistant depression patients who participated in their acute and longitudinal pivotal trials, and compared their outcome with unipolar treatment –resistant depression patients in the same trials.

> Of 235 participants enrolled in the acute study, 25 (11%) were diagnosed with DSM-IV bipolar I or II disorder. A sham-controlled 12-week trial of VNS preceded 2 years of open treatment. Bipolar and unipolar subjects were compared on baseline characteristics as well as acute and long-term outcomes. At baseline, bipolar TRD was as severe as unipolar TRD but with depressive episodes of shorter duration and more failed antidepressant trials per year. Acute, 1-year, and

> 2-year outcomes were similar for both groups, even when the definition of response for bipolar TRD was expanded to include lack of manic symptoms. The study reported that 33% of patients with unipolar depressive symptoms and 38% of patients with depressive bipolar disorder demonstrated a response at 24 months compared with baseline. VNS short and long term effects on bipolar and unipolar TRD were similar. (Nirenberg, et al, 2008, pp. 455)

One limitation to this study includes the fact that some of the participants were diagnosed with an Axis II disorder, while others were not. Additionally, other psychosocial confounding variables were not taken into consideration, including whether or not the participants were involved in concomitant psychotherapy during the study.

Other Clinical Trials

The following clinical trials entail the investigation of the effects of VNS on anxiety disorders, bipolar disorder, treatment resistant depression and brain derived neurotrophic factor. While these trials are small, and some have not been replicated, there is an interest and preponderance from the research community that VNS may be associated with antidepressant and antianxiolytic effects. These studies provide additional support for the use of VNS in the RAD population, again, because of the conjecture that VNS may have effects on the structures and neurotransmitter systems associated with mood disorders and anxiety.

There was one pilot study located of the effects of VNS on anxiety disorders (OCD, panic disorder and PTSD) by George, et al. (2008), and showed moderate symptom improvement during acute treatment.

Several of these researchers have been a part of research on the effects of VNS in treatment resistant depression, and are documented in this paper. Previous works by Ninan in which patients reported anxiolytic effects were reported to have occurred in the following two studies by Rush, et al. (2005) and George, et al. (2005); however, the anxiolytic effects were not overtly documented in either of the articles.

On the basis of reports of anxiolytic effects of patients treated for depression (in these researchers previous work by Ninan, personal communication, (written July 15, 2007), along with reports of anxiolytic effects in patients with epilepsy, these researchers organized an open-label pilot acute trial (12 weeks) of adjunctive VNS in conjunction with stable medications, followed by long term follow up, to assess the safety and potential efficacy of VNS for patients with treatment resistant anxiety disorders (George, et al, 2008). Included in this study were 10 adult patients with OCD, panic disorder, or PTSD, who had failed 4-weeks of medication trials as well as cognitive behavioral therapy. Six of the patients had OCD diagnoses.

> Efficacy and safety data were gathered at 2 baseline visits and at post-implantation weeks 1 and 2 (recovery period), weeks 3 and 4 (stimulation adjustment period), and weeks 5, 6, 8, 10, an 12 (fixed-dose stimulation period). Clinical assessments of anxiety symptoms included the Hamilton Anxiety Rating Scale (HAM-A), and the Yale Brown Obsessive Compulsive Scale (Y-BOCS). The 30-item Inventory of Depressive Symptomology-Self Report (IDS-SR30) was used to measure self-reported depressive symptoms. The Clinical Global Impression Improvement and Severity Scales (CGI-I) and (CGI-S) were used to

assess overall symptom severity and change. Function al outcomes (quality of life) were assessed using the Medical Outcomes Study Short Form-36 (MOS SF-36). The primary outcome measure for all patients was the categorical classification of response, defined a priori as a 50% or greater reduction at exit relative to the average of the HAM-A scores obtained at the two baseline (pre-implantation) visits an a score of 1 or 2 on the CGI-I ("Very much improved" or "Much improved"). Response among patients with OCD was defined as a 25% or greater reduction relative to the average of the Y-BOCS scores obtained at baseline. Of the 11 patients, 10 were included in this study, as one patient who became more anxious about the VNS device as surgery approached was discontinued from the study prior to being implanted. In general, side effects in this group paralleled those reported in prior VNS clinical studies.

At the conclusion of the acute phase, 1 of the 9 patients met the a priori definition of response (>50% reduction in the HAM-A score and a score of 1 or 2 on the CGI-I). The mean change in score on the HAM-A was a reduction of 8.1 from baseline. Three of nine patients (33.3%) had a 50% or greater improvement in HAM-A scores alone from baseline (7.7-73.9, Clopper-Pearson "Exact" confidence interval [CI]). Among the 6 patients with OCD, the mean change in score on the Y-BOCS was a reduction of 5.7 from baseline. Three of these patients (50.0%) were responders based on a 25% or greater improvement in Y-BOCS scores from the baseline (15.2-90.8, CI). The confidence intervals for these last two assessments contained 50%, which implies that the percentage of

> responders was not significantly different from 50% and therefore is not different from the percentage of non-responders. The efficacy –longitudinal profile indicated that with the HAM-A, there was some improvement in anxiety ratings over time with statistically significant improvements at 14 out of the 18 quarters. The response rates increased gradually over the 18 quarters of the study, with least square means (LS) of 0.31 after quarter 1 and 0.48 after quarter 18. The minimum was 0 after quarter 3, and the maximum was 0.52 after quarter 16. None of the response rates were statistically significant. The efficacy-longitudinal profile also indicated that there was some improvement in the Y-BOCS scores over time with statistically significant improvements at 7 out of the18 quarters. Quarterly improvement from baseline for the SF-36 Mental Component was statistically significant in 6 of the 18 quarters. (George, et al, 2008, pp 113-118)

Limitations of this study include the fact that it was a very small mixed sample of patients, and that the patients did not need to be treatment resistant to participate in this trial, as in most trials with VNS.

One study was found that investigated the effects of VNS on serum BDNF concentrations in depressive patients (Lang, Bajbouj, Gallinat & Hellweg, 2006). This study included 10 VNS patients and 14 rTMS patients (age 46.29 ± 13.2), during a 4-week treatment period. Inclusion criteria were a diagnosis of unipolar major depression, and participants were able to have a concurrent psychotropic medication regimen, as long as it was constant 4 weeks before inclusion. One of the 10 VNS patient was free of

psychotropic medications 4 weeks before inclusion. Patients were administered the Hamilton Depression Rating Scale (HAM-D) and Montgomery Asberg Depression Rating Scale (MADRS) prior and subsequent to the 4 week treatment period. Results indicated that BDNF serum levels in the VNS group amounted to 23.252 ± 5.831 ng/ml at baseline and 24.497 ± 4.534 ng/ml after 10 weeks. BDNF (n=10, Z= -0.663, and p=0.508), serum levels did not change over the VNS treatment period. Limitations to this study include the very small sample size, and lack of blinded assessment, which limits the validity and reliability of this study.

In an open pilot study of VNS in adults (18-70 years of age) by Sackeim, et al. (2001), 60 patients with treatment resistant major depressive episodes, or bipolar depressive episodes, who had not responded to two medication trials from different antidepressant classes completed a 2 week single blind recovery period (no stimulation) followed by 10 weeks of VNS. Efficacy and safety data were gathered at the two baseline visits and at weeks 1 and 2 (recovery period), 3 and 4 (stimulation adjustment period), and weeks 5, 6, 8, 10, and 12 (fixed dose stimulation period) after implantation. Clinical assessments of depressive symptoms included the Hamilton Depression Rating Scale (HRSD), the Montgomery-Asberg Depression Rating Scale and the Clinical Global Impression-Improvement Score. Concomitant ECT, investigational drugs, or treatment with another investigational device was not permitted. Patients could receive antidepressant, mood stabilizer, or other psychotropic medications as long as the same medication types and doses were maintained during the baseline period and for 12 weeks following implantation. The only psychotropic medication that could be added during the

trial was Lorazepam (up to 3mg/day) for anxiety and/or insomnia as needed. The total sample averaged statistically significant improvement in HRSD (p=<.0001), MADRS (p=<.0001), CGI severity scores (p=<.0001), and Global Assessment Functioning (GAF) (p=<.0001) at exit of this acute study. This study was flawed by the concurrent psychotropic medication therapy, and lack of control group.

The efficacy and safety of VNS was also assessed by Bajbouj, et al. (2010), in patients with treatment resistant major depressive disorder. This naturalistic, non-randomized, open label study included 74 European patients. Psychometric measures were obtained after 3, 12, and 24 months. VNS was used as an adjunctive treatment to psychotropic medications and the number of concomitant medications taken at baseline were compared to those taken after 3, 12, and 24 months of VNS.

> The primary outcome measure was improvement from the baseline Hamilton Rating Scale for Depression (HRSD) over time, and the secondary outcome measures were changes in scores on the Montgomery-Asberg Depression Rating Scale (MADRS), the Inventory of Depressive Symptoms-Self Report (IDS-SR), Clinical Global Impression Scale Severity (CGI-S), and the Clinical Global Impressions Improvement. These measures were conducted at 3, 12, and 24 months. Response was defined a priori as a 50% or greater reduction in the HRSD scores compared with the mean score of two baseline visits. For secondary outcomes, response was defined as a reduction of 50% or more in the score compared with baseline for the MADRS or the IDS-SR. Remission was defined a priori as a score of <10 for the HRSD, <10 for the MADRS< or <14 for the IDS-

SR. Mixed model repeated measures analysis of variance (ANOVA) revealed a significant reduction in the primary efficacy measure (HRSD) for observed cases (OC) and last observation carried forward (LOCF). In the 3 month versus 12 month comparison (p=0.003, OC; p=0.018, LOCF), and 3 month versus 24 month comparison (p=0.010, OC; p=0.016, LOCF). In the secondary efficacy measures, comparisons of improvement in the scores were significant for the MADRS at 3 versus 24 months (p=0.013, OC; p=0.014, LOCF); for the IDS-SR at 3 versus 12 months (p=0.047, OC) and 3 versus 24 months (p=0.025, OC; p=0.020, LOCF); and for the CGI-S at 3 versus 12 months (p=0.024, OC) and 3 versus 24 months (p=0.007, OC; p=0.009, LOCF). None of the CGI-I comparisons were significant. No statistically significant differences were found at 3, 12, or 24 months for the number of concomitant antidepressant drugs (p=0.62; mean/median 3 months=1.3/1.0; 12 months=1.3/1.0; 24 months= 1.2/1.0), or antipsychotic drugs (p=0.90; mean/median 3 months=1.5/1.0; 12 months=1.3/1.0; 24 months= 1.3/1.0). (Bajbouj, et al, 2010, pp 6 and 9)

Voice alteration, cough, and pain were the most frequently reported adverse effects. Two patients committed suicide during the study; both were women. One woman had a history of 18 previous suicide attempts and had been responding to VNS treatment while the other had no history of suicide attempts and had not responded to treatment. No other deaths were reported. According to the researchers of this study, the results of this 2-year open label trial suggest a clinical response and a comparatively benign adverse effect profile among patients with treatment resistant depression. Limitations to this study

include the researchers having a relationship with the manufacturer, and a disclaimer noting that Cyberonics provided assistance with obtaining analysis and formatting the transcript.

In a European multi-center, open label study of VNS in treatment-resistant depression by Frick, et al. (2006), VNS was found to be efficacious in a substantial number of treatment resistant depressed patients. Additionally, the benefit occurred in an increasing number of patients over time. Patients were implanted with the VNS system and followed over one year. Severity of depression was assessed by the Hamilton Rating Scale of Depression (HRSD) and a priori definitions were used to define response (>50% reduction in baseline HRSD score) and remission (HRSD score <10). The severity of depression was assessed after three months of VNS (acute study period), after 6 months, after 9 months, and after 12 months (long term period) of VNS and compared to the baseline severity of depression. Baseline score on the HRSD averaged 34.8 (SD ±5.8) , indicating severe depression. The severity of depression measured by the HRSD diminished significantly during the first year of VNS ($F(5)=40.4$, $p=0.000$), the score averaged 21 (SD ±12) after 3 months, 20 (SD±12) after 6 months, 18 (SD±11) after 11 months and 15 (SD±10) after one year. At the end of the acute study period, (3 months), 44% of the patients met criteria for response. This rate remained stable after 6 months (40%), then increased and reached 49% after 9 months, and finally reached 58% after one year of VNS. At the end of the acute study period, 21% met the criteria for remission, 25% after 6 months, and 35% after one year of VNS. In this sample, median time to response was 6 months, and 48% of patients showed sustained response, and once they

responded to VNS they remained responders. The percentage of patients with fluctuating response was 33% and 19% of the patients did not meet criteria for response any time during the first year of VNS. Because this study only used one instrument (the HAMD scale) to assess the outcome, and did not include a sham control, a placebo effect may have confounded the results. Other limitations include the lack of blinded assessment, which limits the validity and reliability of this study. The authors of this study also have a financial relationship with the manufacturer.

A two-year outcome of the European VNS study in a sample of 38 patients suffering from treatment resistant depression by Frick, Kayser, Bewernick, Axmacher & Schlaepfer (2007), VNS was found to be effective in reducing depressive symptoms in this population. In this study, 38 patients were treated with VNS and completed the 2-year follow up study period. Severity of depression was assessed by the HRSD and a priori definitions were used to define response (>50% reduction in baseline HRSD score) and remission (HRSD score <10). Severity of depression was rated every 3 months between the 3rd and 24th month after VNS implantation and was compared to baseline severity. Rates of response after 3, 12, and 24 months of VNS were analyzed. Pattern of response during the two years of VNS were defined: patients were classified as sustained responders (early: onset at 3 months, late: onset at ±12 months) if after onset of response no relapse occurred during the first two years of VNS.

Patients never meeting criteria for response during the two years were classified as non-responders and patients experiencing a relapse after responding to VNS during the two years of VNS were classified as transient responders. Rates of response (remission)

were as follows: 45% (21%) after 3 months, 54% (37%) after 12 months and 50% (37) after two years of VNS. The baseline HRSD score of 34.7 (±5.8) decreased significantly to 20.9 (±11.6) after 3 months, 16.1 (±11.2) after 12 months, and 17.9 (±12.6) after 24 months of VNS (ANOVA, F(3)=33.908; p=0.000). 34% showed sustained response, 16% with early onset and 18% with ate onset. The percentage of patients with transient response was 50% and 16% of the patients did not meet criteria for response any time. Because this study only used one instrument (the HAMD scale) to assess the outcome, and did not include a sham control, a placebo effect may have confounded the results. Other limitations include the lack of blinded assessment, which limits the validity and reliability of this study.

In an open-label, non-randomized 24 month outcome study of 74 adult patients with unipolar or bipolar depression across 11 study centers in Europe by Allen (2008), outcome analysis showed an increasing number of patients who met criteria for response and remission over the 24 months. Additionally, the improvement from baseline in mean assessment scores also improved over time. In this study, stimulation began 2 weeks post-surgery, and parameters were also adjusted to maximum tolerance over a 2-week period. Parameters were held constant for 8 weeks, which marked the end of the acute phase of the study.

Concomitant antidepressant and antipsychotic medications were allowed if administered according to the study protocol and held stable for 4 weeks before the first baseline visit and during the acute phase. Patients were followed up for a total of 24 months. Psychiatric assessments included the HRSD and the MADRS. The HRSD was

the primary efficacy variable; patients who scored 10 or less on the HRSD were considered remitters, and patients whose scores improved by 50 or more were considered responders. The number and percentage of patients who met the criteria for response of VNS after 3 months was 26 patients (35.1%), after 12 months was 33 patients (44.6%), and after 24 months was 34 patients (46%). The number and percentage of patients who met the criteria for remission after 3 months was 13 patients (17.6%), 22 patients after 12 months (29.7%), and 24 patients after 24 months (32.4%). This study was limited by the use of concomitant psychotropic medications.

A prospective nonrandomized controlled study of 9 patients suffering from treatment resistant depression evaluated the clinical aspects and cost effectiveness of VNS treatment. In this 12-month study by Sperling, et al. (2009), improvements in depression were measured through the HDRS and changes in duration of depression related hospitalization and the number of psychiatric treatments per year were also evaluated. The study enrolled 9 patients receiving VNS as an adjunct to pharmacotherapy and psychotherapy and 9 patients (sex and age matched) to the VNS group, who continued pharmacotherapy and psychotherapy but did not undergo device implantation.

> Compared with baseline values in the HAMD scale (mean 23.7; SD 2.4), there was a significant ($t=14.5$, $df=8$; $p<0.001$) improvement in symptoms after 12 months stimulation (mean 10.2; SD 2.4). There was no significant change in the control group. VNS also significantly decreased the yearly number of days hospitalized from 65 to 44, while hospitalization rate in the control group did not change. VNS also reduced the number of psychiatric treatments from 33 to 24 per

> year, and drug treatment from 4 to an average of 3 psychotropic drugs. There was no statistically significant change in these parameters for the control group. (Sperling, et al, 2009, pp 85)

Because this study only used one instrument (the HAMD scale) to assess the outcome, and did not include a sham control, a placebo effect may have confounded the results. Additional limitations to this study include the very small sample size, and lack of blinded assessment, which limits the validity and reliability of this study.

In a multicenter, double blind study by Aronson, et al. (2013), the researchers compared the safety and effectiveness of different stimulation levels of adjunctive VNS for the treatment of treatment resistant depression. This study consisted of 331 patients who were randomized to one of three dose groups: Low (0.25 mA current, 130 μs pulse width), Medium (0.5-1.0 mA, 250 μs), or High (1.25-1.5 mA current, 250 μs). A highly treatment resistant population (>97% had failed to respond to >6 previous treatments) was enrolled. Response and adverse effects were assessed for 22 weeks (end of acute phase), after which output current could be increased, if clinically warranted. Assessments then continued until week 50 (end of long-term phase). During the acute phase, all groups showed statistically significant improvement on the primary endpoint (change in Inventory of Depressive Symptomology-Clinician Administered Version (IDS-C), but not for any between-treatment group comparisons. In the long-term phase, mean change in IDS-C scores showed continued improvement. Post-hoc analyses demonstrated a statistically significant correlation between total change delivered per day

and decreasing depressive symptoms, and analysis of acute phase responders demonstrated significantly greater durability of response at medium and high doses than at the Low dose. The researchers concluded that TRD patients who received adjunctive VNS showed significant improvement at study endpoint compared with baseline, and the effect was durable over 1 year. The lack of a controlled standard treatment compare group limited the conclusions of this study.

As per United Healthcare Medical Policy on Vagus Nerve Stimulation (2014), a systematic review on the safety and efficacy of VNS in treatment resistant depression was conducted by (Daban, martinez-Aran, Cruz & Vieta (2008). The three major databases (Medline, Psychological Abstracts and Current Contents) were reviewed beginning January 2000 and ending in September 2007.

> Ninety-eight references were found, but only 18 add-on studies met the required quality criteria and were included in the review. Only 1 double blind RCT was available, and therefore, a meta- analysis was not feasible. In a majority of the preliminary open studies selected for the review, VNS was associated with a significant reduction of the depressive symptoms (primary outcome: Hamilton Depression Rating Scale, HDRS) in the short and long term. Unfortunately, the only double blind study gave rather inconclusive results. Generally, VNS is reported to be a safe and feasible procedure. However, despite the promising results reported mainly in these open studies, further clinical trials are needed to confirm its efficacy in major depression. (UHC, 2014, pp. 7)

A meta-analysis was performed by Berry, et al. (2013), to compare response and remission rates in depressed patients with chronic treatment resistant depression, treated with VNS plus TAU, or TAU alone. The 6 clinical studies included in the meta-analysis were 2 single arm studies of VNS+TAU, a randomized trial of VNS + TAU verses TAU, a single arm study of patients who received TAU, a randomized trial of VNS + TAU comparing different VNS stimulation intensities, and a nonrandomized registry of patients who received either VNS+TAU or TAU alone (all documented in the preceding paragraphs).

Response was based on the Montgomery-Asberg Depression Scale (MADRS) and the Clinical Global Impression Scale's Improvement subscale (CGI-I), as these were two clinician related measures across all or most studies. Outcomes were compared from baseline up to 96 weeks of treatment with VNS + TAU (n=1035) versus TAU (n=425). MADRS response rate for VNS +TAU at 12, 24, 48 & 96 weeks were 12%, 18%, 28%, and 32% versus 4%, 7%, 12%, and 14% for TAU. The MADRS remission rate for VNS + TAU at 12, 24, 48, and 96 weeks were 3%, 5%, 10%, and 14& versus 1%, 1%, 2%, and 4% for TAU. Adjunctive VNS therapy was associated with a greater likelihood of response and remission compared with TAU. For patients who had responded to VNS + TAU at 24 weeks, sustained response was more likely at 48 weeks and at 96 weeks. Similar results were observed for CGI-response. The authors concluded that for patients with chronic TRD, VNS+TAU has greater response and remission rates that are more likely to persist than TAU. According to the authors, the primary limitation of the meta-analysis involved the individual study designs, that the group TAU data is limited to 2

trials for the CGI-I scale and 1 trial for the MADRS scale; in addition, the nonrandomized study and the randomized, sham-controlled study represent the only concurrent head to head comparisons of VNS+TAU and TAU.

Final Thoughts

Studies and their limitations were included in this chapter and presented in detail, in an effort to provide additional support for the use of VNS in the RAD pediatric population, in regard to safety, tolerability, increase in quality of life, and its antidepressant and anxiolytic effects. Because there are numerous studies of the use of VNS in the pediatric epileptic population and none in the pediatric psychiatric population, support for the use in the pediatric psychiatric population requires a close and almost equivalent comparison. Though statistical significance was not found in every study, and mixed results overwhelmed the entirety of studies, it can be concluded that these studies, in conjunction with human and animal neuroimaging studies and neurotransmitter theories pertaining to the pathophysiology of RAD, depression and anxiety, that VNS may be effective in the treatment of RAD in the pediatric population.

CHAPTER 4. METHODOLOGY

This chapter will provide a step-by-step description and explanation as to how the assessment of RAD will be conducted, and under what circumstances VNS would be indicated, and information about referral source and targeted population.

Referral Source and Identified Population

The state child welfare agencies will be the only source of referral because they have the most appropriate population base for this type of proposed treatment, and the population base is substantial.

The trends in foster care report noted by the U.S Department of Health and Human Services, Administration for Children and Families (U.S Children's Bureau, 2013) indicate that there were 241,000 entries of children into the foster care system in fiscal year 2012. This number is substantial, and results in child welfare agencies being a large referral source.

Child welfare agencies are the most appropriate referral source due to the fact that children in the custody of child welfare agencies already have a substantiated history of abuse and/or neglect as well as an initial bond rupture with their primary caretaker, placing them in a risk category of developing symptoms of RAD. Though there are no current prevalence rates for RAD within our outside the foster care or child welfare systems (APA, 2000; Lake, 2005; Chaffin, et al., 2006), there is research that indicates that children being raised within the foster care system are considered to be at risk for developing RAD (Steinhart, et al. 2012).

Though the primary intention of this research is to explore a new treatment that could be potentially efficacious in the treatment of RAD, an overarching intention is to increase the potential for the permanency of children in care. Research suggests that the majority of parents are already not willing to foster children with psychological or behavioral problems (Cox, et al. 2011), rendering this population difficult to not only place, but also to maintain within a placement which perpetuates and builds upon that child's already disturbed attachment schemas.

Criteria for Inclusion Checklist

The following criteria should be met prior to making a referral:

1. The child must be in the custody of the state welfare agency in the respective state which the child permanently resides, as measured by court order.
2. The child's biological parents should have already had their parental rights legally terminated, as measured by a court order.
3. The child must have a history of grossly pathogenic care, abuse or neglect, and/or early life stress, as measured by the child's primary caretaker having been substantiated of abuse or neglect upon that child, and that child having been removed from his or her primary caretaker(s). Measurements also include all investigative reports and all reports of findings. Investigative reports from any and all initial investigations pertaining to the child's history should include information about referral source and their allegation(s), the child welfare worker's field responses, and interviews with all involved parties including the alleged child victim and the alleged perpetrator. Any medical findings or consults

that were a part of the investigation and assisted in determining a finding should also be included. The findings report must indicate whether the caretaker(s) were substantiated of abuse and/or neglect, and if so, which specific type.

4. The child must be between 4.5 and 6.5 years of age. Though this study includes children 5-7, the age range of 4.5 and 6.5 are recommended in this stage, to provide adequate time for the protracted referral and assessment process.
5. The child must be in foster care, and in the custody of the state child welfare agency which child permanently resides. There is no specific timeframe for which the child should be in placement. This will be measured by a court order.
6. The child must be at risk of not achieving permanency within a foster home as a result of a history of unstable placements secondary to the child's behavioral and/or socio-emotional functioning. This will be measured through documentation of all prior placements, including rationale for removal and re-placement.
7. The child may or may not be on psychotropic or other medications. This will be measured by a written list of current medications by the prescriber, given to the child welfare worker.
8. The child may or may not be involved in ongoing therapeutic intervention. This will be measured through written notification by all therapists regarding their treatment with the child, given to the child welfare worker.
9. Contraindications of VNS therapy include having a history of bilateral or left cervical vagotomy (Marangell, et al. 2007); therefore, a child should not be

referred if either of these disorders exists. Measurement of this should be obtained through the child's medical record, by the pediatrician, given to the child welfare worker.

In the event the child welfare worker can show that the child meets the basic requirements for possible inclusion in the study, the primary child welfare worker should provide the above criteria for inclusion checklist confirming that all basic criteria has been met, and documentation obtained through completion of the above checklist, for review by the assessment team.

Once the assessment team has met and reviewed the documents provided by the child welfare agency, a decision will be made to either begin the formalized process described below, or decline the child for inclusion in the study based on not meeting the above 9 essential requirements.

In the event a decision is made to move forward in the evaluative process, the entire team will meet with the child's caregiver(s) and the primary welfare worker to discuss the impending evaluative process.

Five-Pronged Approach

In order to effectively assess whether a child would be an appropriate candidate for VNS, and to determine whether RAD is the primary diagnosis, a thorough, comprehensive and interdisciplinary evaluation is essential. All aspects of each assessment and follow up procedure will be done on an outpatient basis.

The multidisciplinary and interdisciplinary aspects of the assessment will be comprised of a five-pronged approach: medical examination and clearance by a primary

care physician, an individual biopsychosocial evaluation by a licensed clinical social worker (LCSW) or licensed professional counselor (LPC) clinician, an independent evaluation by a neuropsychologist, a biochemical analysis by a PhD level biochemist, and surgical clearance and application of the VNS by a neurosurgeon. All five levels of the multidisciplinary team are required, and the details pertaining to each discipline's evaluations and assessment processes will be provided in the upcoming sections. The convergence of the five specialties of this interdisciplinary team will provide a solid base for a reasonable, evidence-based argument in deciding treatment indications, recommendations, differential diagnosis, and implementation of VNS.

The rationale of this interdisciplinary approach is to obtain a vigorous and holistic conceptualization of the child and his or her environment, experiences, developmental neurobiological functioning, and physiological and psychological functioning. A comprehensive approach of the child, family and the broader community will be taken into account, and is regarded as an integral aspect of this assessment. While the number of experimental studies evaluating the impact of enhanced collaboration on patient outcomes is relatively small, a body of experimental literature supports the proposition that collaborative mental health care results in better practices and outcomes (Craven & Bland, 2006).

The primary goal of utilizing the interdisciplinary approach is for each discipline to work together as a fluid team, and for each discipline to utilize a standardized structure in their assessment process. This procedure will not only help the child and the child's caretaker(s) in regard to permanency and standard of living, but it will also ensure that

this research is conducted in the most empirically sound manner. The standardized assessment structure for each discipline will include specific behavioral checklists, a semi-structured interview tool, a neuropsychological battery, biochemical parameters, and a differential diagnostic instrument, to ensure standardization across all variables. Details in regard to these assessments will be discussed in the proceeding sections, under each specific discipline's section.

A secondary goal is for the child's caretakers and child welfare personnel to have a clearer understanding of the neurobiology behind RAD and its manifestation of symptoms. At specific stages during the evaluative process, meetings that the team has alone, and in conjunction with the child's caretaker(s) and primary child welfare worker will take place. Team meetings and caregiver-team meetings will both serve as a part of this interdisciplinary approach, and will also add an undercurrent of education for the child's caretaker(s) and child welfare worker. During these meetings, results of evaluations and assessments will be discussed and the expert in each discipline will take the lead on providing the educative aspects of their specific assessment, and its applicability to the child. Additional details pertaining to team meetings and caregiver-team meetings will be described later in this chapter.

The overarching intention of utilizing this approach is to enhance the prospect that this vulnerable population will have higher quality outcomes, and that better practices in the field of neuropsychiatric disorders will reverberate.

Medical Exam and Clearance

Prior to a child being fully considered as a candidate in this study, a comprehensive and thorough history and physical will be obtained. The evaluator of this aspect of the assessment will be a general physician.

The purpose of a medical examination and medical clearance are to ensure the patient has no medical illness. A child will be considered to be medically clear in the following two situations: when the patient has been found to have no medical illness, or, a medical illness is known to be present, but is not thought to be the primary cause of the patient's symptoms (Reeves, Perry & Burke, 2010).

The general format most commonly used for a history and physical are listed in Appendix A (Blumenfeld, 2010), and will be required to be used for standardization purposes.

In the event that the physician renders the child to be medically cleared, the next step in the assessment process will be commenced. The child's entire file, including the results of the medical examination, will be forwarded to the next evaluator on the team. In the event the child is not considered medically cleared, the next step in the evaluative process will not be commenced, and a review by the entire evaluative team will occur to discuss implications of the medical findings.

Biochemical Evaluation

The biochemical evaluation process includes assessment of the HPA tone through the measurement of cortisol. The purpose of measuring cortisol levels of children included in this study is to reveal characteristics of each child's stress regulatory

functioning, and to have a corroborating biomarker in the assessment of RAD. The cortisol samples can begin to be collected immediately after medical clearance, and simultaneous to the biopsychosocial evaluation.

A PhD level biochemist will be the professional involved in the biochemical evaluation portion of the assessment. A PhD biochemist is recommended over a master's level biochemist due to the fact that the biochemist will be working independently, and will not have supervision, or collaboration with, another biochemist. It is expected that the biochemist will be an expert in his or her discipline.

Salivary Cortisol

Salivary cortisol is a measure of biologically active free cortisol, follows the same diurnal rhythm of serum cortisol, and has a strong correlation to free cortisol measured in plasma and serum (Faravelli, et al. 2012). Salivary cortisol is preferred to be collected over serum cortisol due to the fact that saliva is an easily obtainable biofluid and a noninvasive source for evaluating the HPA tone. It is also amenable to timed sample collections in the free-living state for at least 1 week without the need for medical personnel, and can be at room temperature (Golden, Wand, Malhotra, Kamel & Horton, 2011). This method will prove less intrusive to this population and their caregivers in comparison to blood samples, which require venipuncture and several trips to the office to collect samples.

Salivary cortisol has been used extensively as a biomarker of stress in a research setting, especially in studies examining psychological stress (Inder, Dimeski & Russell, 2012), and are used as a result of close links between the HPA and cortical and limbic

structures, which are important mediators of the subjective psychological stress response (Hellhammer, Wust & Kudielka, 2009). Upon review of the literature, there has been one study measuring cortisol secretion in children with symptoms of RAD; however no association was found between cortisol secretion and symptom scores for psychopathology (Kocovska, et al. 2013). On the other hand, there have been a copious amount of studies that have found associations between cortisol secretion in children with attachment problems, abuse/neglect and early life stress. In a recent meta-analysis of 30 published findings on cortisol response to stressors in 0-5 year old children who were already exposed to a negative environmental influence post-conception, 27 studies reported a significant cortisol changes (Hunter, Minnis & Wilson, 2011). Of those 30 studies, 14 of the studies included children who were exposed to abuse, neglect and/or had attachment problems. In support of these studies, under experimental conditions, episodes of human maternal separation in healthy 9-month-old children have also been found to elicit HPA activation (Turner-Cobb, 2005).

Of relevance is that in all of these studies, none documented the salivary cortisol expected value ranges, and was there was also no documentation of the salivary cortisol results of the participants. A normal range for cortisol responses in infancy and childhood is not well established due to great variation between studies (Hunter, et al. 2010). Given that significant differences in HPA function are detectable in both experimental studies and under naturalistic conditions for normal healthy populations in children, there is no agreement in the literature as to what is considered a normal range of salivary cortisol (Turner-Cobb, 2005). What has been agreed upon is that differences detected in the

direction of change in cortisol secretion appear to reflect the nature of the maltreatment, psychological diagnosis, timing of maltreatment, and the child's own physiology (Nelson & Spieker, 2013).

Fundamentally, there is no guidance from previous studies in children exposed to abuse/neglect or with attachment issues, and there has not been an agreement in the literature in regard to expected value ranges, cortisol ranges, and direction in cortisol for this population. In an effort to resolve this complication for the purpose of this study, an extensive review of the research has been conducted to locate FDA-approved salivary cortisol expected ranges.

Upon conducting this research, it was found that up until 2003, there were no salivary cortisol expected value ranges to assist in diagnosing Cushing syndrome, which is a syndrome associated with prolonged exposure to inappropriately high levels of cortisol (Raff, Homar & Skoner, 2003). Upon further investigation, only one FDA-approved cortisol immunoassay was found, marketed by Salimetrics, LLC, through Penn State University. The expected value ranges of salivary cortisol are included in this immunoassay package, and are currently used in the diagnosis of Cushing syndrome.

The expected cortisol salivary ranges noted by the manufacturer are as follows: AM for children ages 2.5-5.5 are 0.060-0.700 and PM ranges are 0.08-0.660. For children ages 8-11, the ranges are 0.112-0.904 and PM ranges are ND-0.249. It is clear that there are no ranges for children between the ages of 6.0 and 7.5, leaving out range expectations for children who are between the ages of 6.0 and 6.5 included in this study. Children who fall within this category of age ranges (6.0 and 6.5) will follow the expected cortisol

ranges stipulated for the 2.5-5.5 age range, as the age of 5.5 is closer to 6 and 6.5 than the age of 8.

As per the letter written to Penn State University by the FDA (FDA, 2003), the High Sensitivity Cortisol Enzyme Immunoassay Kit (HS-Cortisol kit) was determined to be substantially equivalent for indications for use and to be legally marketed. According to the manufacturer, the HS-Cortisol kit is designed for the quantitative in vitro diagnostic measurement of salivary cortisol, and has not been withdrawn from any country for issues related to effectiveness or safety (Salimetrics, LLC, 2003).

Because the HS-Cortisol kit was approved by the FDA, and includes a standardized expected value range along with the associated age ranges, this kit will be used by the biochemist for all salivary cortisol samples. This will also maintain the standardization format of all assessments being utilized in this study.

Timing and Method of Collection

Salivary cortisol follows the same diurnal pattern across age groups, sharply increasing within one hour after waking and steadily declining thereafter, until reaching the lowest level in the late evening hours (Piazza, Charles, Stawski & Almeida, 2013). The times of 8AM and 11PM salivary cortisol collection is recommended due to the assumption that individuals with high cortisol burden will have elevated cortisol levels at both the peak and lowest of the cortisol circadian rhythm (Golden, et al. 2011). A second reason for collecting two samples per day is because collecting multiple salivary samples will account for within-individual differences. Additionally, the manufacturer of the H-S

Cortisol kit has both AM and PM expected ranges (Salimetrics, LLC, 2003), in line with the frequency of samples required for this study.

The caretaker(s) can easily gather both AM and PM samples at home, and keep the samples at room temperature for no longer than one week (Golden, Wand, Malhotra, Kamel & Horton, 2011). The saliva sample may be collected by drooling or through the use of absorbent swabs that are placed into the child's mouth until saturated (Inder, Dimeski & Russell, 2012). The manufacturer of the HS-Cortisol kit is in support of the literatures method of collection and storing (Salimetrics, LLC, 2003). The caretaker can choose to either mail the samples, or drop them off in person directly to the biochemist. Once the biochemist has obtained the 7 days worth of AM and PM cortisol samples, the results will be interpreted and placed in the child's file.

Biopsychosocial Evaluation

One of the most comprehensive, integrative and well-known approaches to conceptualizing the mental health assessment process is through conducting a biopsychosocial evaluation. The essential aim of the assessment is to gather information and objective data, and to form a therapeutic relationship within which the problem can be understood and progress can be made toward solving it.

The biopsychosocial approach is considered to be the cornerstone in this particular assessment process due to the nature of RAD and the etiology of its contributing factors. Of utmost relevance to this type assessment is the fact that a biopsychosocial evaluation stresses the importance of a comprehensive, systemic perspective on human development and functioning, and emphasizes a holistic

integration of biological, psychological, and sociocultural factors when attempting to understand human psychology (Meyer & Melchert, 2011).

At the heart of a biopsychosocial assessment is being able to cross-situationally evaluate a child's functioning across as many domains as possible: school, home, and within the community. All of these aspects of the biopsychosocial evaluation will be obtained and thoroughly conceptualized by an LCSW or LPC clinician. Either an LCSW clinician or LPC clinician is recommended due to the fact that they are independently licensed to practice and are considered experts within their respective fields.

The first part of the biopsychosocial evaluation will be to conduct semi-structured interviews with the primary caregiver(s). During the intake assessment, the caretaker(s) and the child will all be present; however, the child will not be interviewed independently, but will be present for observation purposes. It is recognized that the ideal assessment would include both interviews with the caregiver(s) and the child as informants; however, interviews of children themselves when younger than 7 years of age are not feasible because they have not yet mastered multiple types of skill needed for this task (Scheeringa & Haslett, 2010).

The purpose of observing the child is to observe his or her behaviors, responses, and interaction between caretaker(s), and to obtain a mental status. Observation and various interactions with the child during the interview with the caregiver(s) will provide the clinician with insights into the relationship and attachment dynamics.

Standardized or structured interviews will not be utilized at any time during the biopsychosocial evaluation, as they are primarily based on questions, while the

observations of the assessor are of less importance (Linden & Muschalla, 2012). A semi-structured interview format will be used in this research study as an informal evaluative tool to obtain pertinent biopsychosocial information, and as a supporting mechanism in the observation aspect of the assessment. Semi structured interviews are widely used in qualitative research (Harvey-Jordan & Long, 2001), elicit a sense of therapeutic alliance, and involve the use of pre-determined topics where the clinician will be free to seek clarification. In order to provide as much standardization as possible through the use of the semi-structured interviewing format, an interview framework will be provided to the clinician to ensure all information is obtained. This format can be found in Appendix B (Sadock & Sadock, 2007; Cooper & Lesser, 2005).

Collateral Contacts

Phone or in person interviews will be conducted with all current caregiver(s), current treatment provider(s), previous caregiver(s) and treatment provider(s). The goal in making all of these contacts is for the clinician to gather as much developmental, behavioral, socio-emotional, relational and historical information pertaining to the child as possible, which will provide important insights into attachment and related resiliency or vulnerability factors that may have impacted the functional development of the child.

All pertinent information will be obtained through using the same semi-structured approach discussed above, while using the framework provided in Appendix B to ensure all information is obtained. It is recognized that using this same framework for interviewing all collateral contacts may seem redundant; in spite of this, conflicting information is equally as clinically relevant as corroborated information and facilitates in

providing a comprehensive picture of the child in his or her environment. This also supports the standardization of the interview process across domains.

Child Behavior Checklist and Teachers Report Form

The clinician will provide a standardized rating scale, the Child Behavior Checklist (CBCL) to the caretaker(s), along with the Teachers Report Form (TRF) to the teachers or daycare workers who have interaction with the child. The aim is to gather pertinent behavioral and socio-emotional functioning information, which can be compared across domains. These instruments can be scored, interpreted and administered by a masters level clinician (Christenson, n.d), and therefore, will be the responsibility of the LCSW or LPC clinician.

As noted earlier, there are currently no validated instruments for assessing or diagnosing RAD (Hardy, 2007; Chaffin, et. al 2006). Despite this noteworthy concern, rating scales represent an empirically based class of assessment instruments and are the most efficient and effective means to describe children's social and emotional functioning (Konold, Walthall, Pianta & Virginia, 2004), and the utilization of a structured rating scale to obtain cross-situational data is an imperative aspect in the assessment of young children. Having taken the validity and reliability issues into consideration in reference to there being no valid RAD rating scales, and upon a review of the literature for the most relevant rating scale to be utilized with this population, both the CBCL and the TRF appear to meet the requirements necessary to meet the needs of this specific assessment process. In support for the use of this instrument with this population, the California Evidence-Based Clearinghouse for Child Welfare (2014) has

reported that the CBCL and TRF would be appropriate for use with children and caretakers in the child welfare system.

Both the CBCL and the TRF were designed to define child behavioral problems and social competencies in a standardized format (Freeman, n.d) through the use of empirically based syndrome scales and DSM-oriented scales. Both the CBCL and the TRF include assessment forms for both the preschool age (1 ½-5 years) and school age (6-18 years) children, and both should be available for use since the age range of this proposed study includes children ages 4.5-6.5 years.

The DSM oriented diagnostic scales are not derived directly from problem scores obtained from standardized assessments of children, while the CBCL syndrome scales are (Achenbach & Rescorla, 2000; Achenbach & Rescorla, 2001). Neither of these instruments will be used to make diagnostic inferences, as neither of these scales corresponds with DSM-IV-TR diagnoses (Ebesutani, Bernstein, et al. 2010). Though the CBCL and TRF will not be able to assist in making formal diagnoses, they will be able to help the clinician identify distinguishing features of each child in terms of problems related by each informant and help with the clinician's own impressions. Additionally, the CBCL in particular will enable the clinician to compare the caregiver(s) descriptions from the CBCL with those obtained from normative samples of children. Both the CBCL and TRF will ultimately assist with outcome assessment in this study, as discussed later in this chapter.

Overall, the CBCL and TRF checklists have become a standard against which many other clinical decision-making tools are compared and has become one of the most

frequently used descriptive tools of child psychopathology researchers. Its psychometric qualities and research base are superior to much of its competition (Christenson, n.d), and the instruments have been utilized in over 1,700 studies (Furlong & Pavelski, n.d). The addition of the TRF provides another essential layer of comprehensiveness to the evaluation, and meets the goal of assessing cross-situationally. These advantages, coupled with their ease of administration and the ability to score with an inexpensive computer program (Drotar, et al. 1995), or by hand, make both the CBCL and TRF instruments advantageous and applicable for use in this study.

Please refer to Appendix C (Achenbach & Rescorla, 2001) for psychometrics of the CBCL and TRF ages 6-18, and Appendix D (Achenhach & Rescorla, 2000; Furlong & Pavelski, n.d) for psychometrics of the CBCL and TRF ages 1 ½ - 5.

Diagnostic Infant and Preschool Assessment

In order to maintain as much standardization as possible in regard to diagnosis, the LCSW or LPC clinician will administer the Diagnostic Infant and Preschool Assessment (DIPA) to the caregiver(s).

The DIPA is an interview for children between 1-6 years of age which assists in diagnosis, and is based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR), and the Research Diagnostic Criteria: Preschool Age (RDC: PA) (Gleason, Zeanah & Dickstein, 2010).

As noted in the previous section, the CBCL and TRF scales do not correspond with DSM-IV-TR diagnoses (Ebesutani, Bernstein, et al. 2010) and are therefore unable to be utilized to assist in formulating a diagnosis.

The purpose of the LCSW or LPC clinician administering both the CBCL as well as the DIPA to the caregiver(s) is to assure the comprehensiveness and validity of differential diagnosis and evaluation of RAD in the form of standardized assessments. A standardized diagnostic instrument is required in this research due to the difficulties in diagnosing RAD as a result of the complexities in ruling out the associated comorbidities of RAD.

As noted earlier, there are no validated instruments for assessing or diagnosing RAD (Hardy, 2007; Chaffin, et. al 2006). Despite this noteworthy concern, standardized diagnostic assessments represent the gold standard in clinical research and operationalize diagnostic criteria to increase the reliability and validity of diagnoses (Rettew, Lynch, Achenhach, Dumenci & Ivanova, 2009). Having taken the validity and reliability issues into consideration in reference to there being no validated instruments for diagnosing RAD, and upon a review of the literature for the most relevant standardized diagnostic tools to be utilized with this population, the DIPA appears to meet the requirements necessary to meet the needs of this specific diagnostic process.

The DIPA is an interview for caregivers of children who are between 1-6 years of age and assists in differentially diagnosing between the following disorders: RAD, obsessive compulsive disorder, generalized anxiety disorder, social phobia, specific phobia, separation anxiety disorder, conduct disorder, oppositional defiant disorder, attention-deficit/hyperactivity disorder, bipolar I disorder, post traumatic stress disorder, major depressive disorder, sleep onset disorder and night walking disorder (Scheeringa, 8/18/2010). Because RAD symptoms are easily mistaken for, and overlap with other

diagnosis features such as with conduct disorder, oppositional defiant disorder, attention-deficit/hyperactivity disorder and social phobia (AACAP, 2005; APA, 2000), the overarching rationale for employing the DIPA is to ensure diagnostic accuracy within these comorbidities. The DIPA was also the only standardized instrument located which assessed for RAD within the age group being studied for this research.

The DIPA can be administered in either a structured or semi-structured format, and because the LCSW or LPC clinicians are considered experts in their field, the semi-structured format will be used during the administration.

The duration of the interview can last from 45 minutes to 90 minutes, and varies significantly (Gleason, Zeanah & Dickstein, 2010) dependent upon each child's unique situation. Psychometrics of the DIPA can be found in Appendix E (Scheeringa & Haslett, 2010; Gleason, et al. 2010; De Young, et al. 2012).

Upon completion of the CBCL, the DIPA, and all of the above interviews, the clinician will submit a formal biopsychosocial evaluation, using Appendix A as a framework. The results of this biopsychosocial evaluation will determine whether or not the child may be an appropriate candidate for further evaluation of RAD. In the event the clinician renders the child as appropriate candidate for further evaluation of RAD, the biopsychosocial evaluation and the rest of the contents of the child's file will be forwarded to the neuropsychologist for review. Determining whether or not a child has RAD is a complicated and tedious aspect of this process due to the limited research on its etiology, diagnosis, course, prevalence and prognosis, and requires further examination and collaboration.

Neuropsychological Evaluation

The purpose of a neuropsychological evaluation is to provide a comprehensive overview of the current functioning of the child, including the uncovering of specific targeted brain dysfunctions, and confirmation of RAD diagnosis. The neuropsychological battery is imperative in the assessment of a child who potentially has RAD, due to its neurobiological correlates and opacity in psychiatric assessment alone.

The neuropsychological assessment of children aged 3-6 has been an understudied area of neuropsychology, specifically in regard to the absence of standardized developmentally suitable neuropsychological instrumentation with appropriate psychometric properties and normative data (Baron & Anderson, 2012).

Upon a thorough review of the literature, there were two neuropsychological assessment batteries that were considered, and appeared to offer reliable and precise measures; the Reitan-Indiana Neuropsychological Battery (RINB) for ages 5-8, and the Developmental Neuropsychological Assessment II (NEPSY-II) for ages 3-12 (Dykeman, 2008).

In regard to normative and demographic data, the NEPSY-II updated many of these features within the past decade (Harcourt Assessment, 2007) and was revised as a result of updated research in neuropsychology, child development and child psychology, with the goals to enhance clinical utility, psychometric properties and usability (Brooks, Sherman & Strauss, 2010). On the other hand, the RINB has not been updated as recently in regard to the same. In addition, the age range that is recommended children be referred for this study is 4.5-6.5, which is outside of the age range for the RINB. In an effort to

make the neuropsychological assessment portion of the evaluative process as standardized as possible, it makes sense for there to be only one neuropsychological battery used on all children referred. It is based on these reasons that the NEPSY-II will be the neuropsychological battery utilized in this research (discussed below).

Though neuroimaging could potentially be beneficial in collaborating the findings of the neuropsychologist, neuroimaging will not be a part of the evaluative process as these techniques are not cost-effective. Additionally, neuroimaging studies in RAD are mixed in regard to morphological changes in the substrates known to be associated with RAD (Hart & Rubia, 2012).

The neuropsychologist will be responsible for conducting the full NEPSY-II neuropsychological battery, including all of the subtests. It is recognized that the NEPSY-II allows for the administration of specific subtests, groups of subtests, or the entire battery (Brooks, et al. 2010); however, in order to offer solid follow-up research, each child will be assessed with all of the subtests to ensure for consistency. The neuropsychologist should formulate an integrative report of all the results of the NEPSY-II, including differential diagnosis, confirm that the child has RAD, and provide recommendation(s) for treatment, including the potential for treatment with VNS. Psychometrics of the NEPSY-II can be found in Appendix F (Kemp & Korkman, 2010; Harcourt Assessments, 2007; Brooks, et al. 2010).

Team Meeting

In the event a child has made it to this stage in the assessment process where all of the evaluations have been completed, a meeting with all five team members will occur. A

team meeting is comprised of all five of the disciplines coming together at one time, with the purpose of reviewing and evaluating each assessment to discuss conceptualizations and the results of their evaluations. During this meeting, the team members will decide whether or not the child will be recommended for VNS treatment.

Determinants for Inclusion in the Study

A child will be recommended for VNS therapy based on specific criteria being met with the CBCL and TRF rating scales, neuropsychological evaluation, biopsychosocial evaluation and biochemical evaluation. With the biopsychosocial evaluation, the clinician must have provided the child with a primary Axis I diagnosis of RAD and the child may or may not have co-morbidities. With the neuropsychological evaluation, the neuropsychologist must have provided the child with a primary Axis I diagnosis of RAD and the child may or may not have co-morbidities. With the biochemical evaluation, the child must have salivary cortisol level results, on average, that fall outside the higher end of the expected ranges for their age group. While the literature is in disagreement about whether cortisol levels in this population should be decreased or increased in comparison to the expected ranges (Hunter, et al. 2010), it is hypothesized by this writer that the population included in this study will have salivary cortisol levels that fall outside the higher end of the expected ranges. Initial support for this hypothesis is based upon several studies that report high cortisol levels among children with disorganized attachment style, the attachment type most associated with RAD (Schore, 2001b; Hardy, 2007; Cornell, 2008), following Ainsworth's Strange

Situation. In contrast, none of these studies found high post-test cortisol levels among securely attached children in response to the Strange Situation (Tarullo & Gunnar, 2006).

With both the CBCL and TRF rating scales for the 1 ½-5 year old population, the criteria for inclusion is a clinically significant score (70+) on the following syndrome scales (there are a total of 7 syndrome scales):

1. Emotionally reactive
2. Anxious/depressed
3. Attention problems
4. Oppositional defiant problems

With both the CBCL and TRF rating scales for the 6-18 year old population, the criteria for inclusion is a clinically significant score (70+) on the following syndrome scales (there are a total of 8 syndrome scales):

1. Anxious/depressed
2. Social problems
3. Attention problems
4. Rule-breaking behaviors
5. Aggressive behaviors

The DSM-oriented scales will not be included in the outcome assessment, as they are not derived directly from problem scores obtained from standardized assessments of children (Achenbach & Rescorla, 2000; Achenbach & Rescorla, 2001). Borderline scores

will not be considered due to the fact that having an Axis I diagnosis of RAD clinically indicates that the child has significant distress or impairment in social, occupational and/or other important areas of functioning.

Referrals for Those Not Participating

In situations where the child has completed all aspects of the evaluation process, appropriate referrals tailored to each individual child will be discussed with and provided to the caregiver(s) and child welfare worker.

Referrals for caregivers may include support groups for foster parents and/or the National Alliance for Mental Illness (NAMI) for various other support services related to living with loved ones who have mental illness.

For the child, referrals to different levels of care are dependent upon severity of symptoms. Referrals for those with less severe symptoms could include referrals to a private practitioner who specializes in child traumatology and family work and/or a private psychiatrist. For others, intensive outpatient programs or partial hospitalization programs may be more appropriate.

Other referrals may also include information for attachment-based therapeutic interventions due to the fact that they have shown some efficacy in regard to enhancing attachment (Zilberstein, 2011; Becker-Weidman & Hughes, 2008; Toth & Gravener, 2012).

Caregiver-Team Meeting

A caregiver-team meeting will take place within one week of the team meeting. Included in the caregiver team meeting are the primary child welfare worker, the

caregiver(s), and members of all five disciplines. During this meeting, results of evaluations and assessments will be discussed and the expert in each discipline will take the lead on providing the educative aspects of their specific assessment, and its applicability to the child. An overall conceptualization will be discussed, along with a recommendation for VNS treatment.

Pre-Surgical Neurologic Exam

This is the last step of the five-pronged assessment, and will only occur in the event it was decided amongst all team members and all other involved parties, that VNS is the recommended level of treatment intervention. The neurosurgery consult will be comprised of an abbreviated neurologic exam, as well as a general medical examination.

As a regular course of pre-surgical intervention, an evaluation by the treating neurosurgeon is required to determine the risk of complication during and immediately after the procedure (Allen, 2011). Risk and complication status will be determined through a physical exam as well as a thorough review of the general physician's findings during the initial medical exam taken place earlier in this evaluative process. Though a medical clearance evaluation was already conducted by the general physician earlier in the evaluative process, due to the protracted length of this process, a second one will be required. The format can be found in Appendix A.

A neurologic exam should always be preformed and interpreted in the context of a more general physical assessment (Blumenfeld, 2010), and will accompany the physical examination.

An abbreviated neurologic exam is recommended because as a part of the detailed nature of the neuropsychological assessment an overall general level of functioning is already known. The abbreviated exam can be preformed in 10 minutes or less. Though there is no standard for a neurologic exam, one located by (Blumenfeld, 2010), is applicable, and can be referred to in Appendix G (Blumenfeld, 2010).

Informed Consent and Authorization for Treatment

In the event the neurosurgeon clears the child for surgery, another interdisciplinary team meeting will take place, and recommendations for treatment with VNS will be officially made. A meeting will be held with all five team members, including the primary child welfare worker and the caretaker(s), and informed consent will be discussed, at length. At this point, an offer will be made to the child welfare worker and the caretaker(s) to proceed forth with implantation of the VNS system.

Because one of the criteria for inclusion in this process is that the child's biological parents rights have previously been legally terminated by means of the court system, and verification has been substantiated through possession of a court order, the biological parents will not be included in the informed consent process.

Legally, the guardian of every child referred for VNS is the state child welfare system in which the child permanently resides. Therefore, because this is the case, the informed consent process must be with whomever the respective child welfare agency deems appropriate to be a part of the informed consent discussion. It will also be up to the child welfare agency who they deem appropriate to sign paperwork and authorization to

proceed forth with the procedure (most likely the child's assigned guardian at litem, and/or the deputy attorney general).

Because the caregiver(s) are an integral part of this process, their inclusion and participation is essential for the benefit of the child and for their own knowledge base, and therefore, the caregiver(s) will be included in the informed consent and authorization process. Additional informed consent and authorization documents will be provided to the caregiver(s).

In regard to this particular situation, there are both legal and best practice issues to take into consideration when it comes to informed consent. It is acknowledged that technically and legally, the state child welfare agency has custody of the child and they are the sole decision makers for the child. On the other hand, when it comes to best practices, it is just as imperative for the caregiver(s) to be in agreement, and to authorize and be provided with informed consent of the procedure.

Children have a right to informed consent, and ethically, must be involved in the informed consent process. Such rights stem from the principles of beneficence and respect for people, which reference that competent people are granted self-determination to the greatest extent possible, and there is an obligation to do no harm (Kanner, Langerman & Grey, 2004). In regard to VNS, there have been no informed consent or authorization parameters located for individuals younger than 18 for VNS, most likely due to the fact that VNS is not currently under consideration for neither psychiatric disorders nor epilepsy in children under 18 years of age.

As a result, the informed consent and authorization process for how this procedure will look, will have to be in compliance within the child welfare agency's respective state and federal regulatory codes, Ethics Review Committee(s), and Institutional Review Board(s). Because of differences in federal and state regulatory codes, and the fact that it is unclear which state this research may be piloted in, examples of an informed consent documents will not be generated at this time.

Informed consent and authorization will be reviewed second and final time 72 hours prior to the procedure. The justification for this second informed consent and authorization process is to be in line with the 72-hour mandatory timeframe devised by the AACAP for the use of ECT in adolescents, as this is the only comparison available in regard to brain stimulation techniques in a population other than adults.

Post-Implantation Procedures and Stimulation Parameters

The child and his or her caretaker(s) will return to the office 2 weeks post-implantation, at which time they will meet with the neurosurgeon who will begin establishing stimulation parameters to the VNS device.

Adjustable parameters include pulse width, signal frequency, output current, signal on time, and signal off time. The FDA has approved VNS treatments in the epileptic adult and child population (12 and older), and for individuals 18 and older with depression (Albert, Cook, Prato & Thomas, 2009). For both of these populations VNS programming parameters have been established, although there are slight variations across studies (Leonard, 2005).

In children 12 years of age and older with epilepsy, typical simulation parameters for VNS therapy are set to an output current 0.25 mA, signal frequency 30 Hz, pulse width 250-500 μsec, stimulation "on" time 30 seconds, and stimulation "off" time of 5 minutes, with the output current generally increased to 2-3 mA as tolerated.

For adults ages 18 older with epilepsy, the typical stimulation parameters for VNS therapy are set to current between 1 and 2 mA, a rate between 20 and 30 Hz, a pulse width of 250–500 μs, and a signal "on" time of 30 s, and a signal "off" time of 5 minutes (Albert, 2009). It is clear that VNS stimulation parameters for adults and children 12 years of age and older are different.

Because VNS has not been approved for the pediatric populations, there are no standard guidelines to follow in this regard. On the other hand, there have been ten studies located, including 1 randomized controlled trial, where VNS has been used in children with intractable epilepsy within the age ranges of 1.4 years of age, through the pre-adolescent stage all the way up to 17 years of age (Yu, et al., 2014; Tanganelli, Ferrero, Colotto & Regesta, 2002; Rossignol, et al. 2009; Rychlicki, et al. 2006; Alexopoulos, et al. 2006; Klinkenberg, 2012; Benifla, Rutka, Logan & Donner, 2006; Elliott, et al. 2011; Majkowska-Zwolinska, Zwolinski, Roszkowski & Drabik, 2012; Colicchio, et al. 2010).

Upon review of the stimulation parameters in these studies, similarities were noted. All studies that documented their frequency parameters used a 20-30 Hz frequency, and all studies that documented their pulse parameters used a pulse of 250-500 μs.

All of the studies used an output of 0.25-0.5 mA, with the exception of one study of 1.4 to 18 year olds, whose output parameter was 0.5mA-2mA (Rychlicki, et al., 2006). All of the studies used an "on" time of 30 seconds, and an "off" time of 5 minutes, with the exception of the study by (Rychlicki, et al., 2006), who used an off time of 3 minutes, instead of 5.

Based upon the above studies in the pediatric epileptic population with regard to stimulation parameters, this study's parameters should be the following: output of 0.25-0.5mA, 30 seconds off 5 minutes on, 20-30Hz frequency, and pulse of 250-500μs. Not only are these recommended stimulation parameters congruent with those used in the pediatric epileptic population but they are also congruent with the FDA's parameters of VNS therapy in children 12 years of age and older. Pulses will be delivered to the vagus nerve 24 hours a day, or until turned off.

Because therapeutic brain effects are gradual over several months (Conway, et al. 2012), with full benefits observed after 6-12 months of stimulation, with sustained efficacy up to 2 years (Mohr, et al. 2011), the length of time of VNS treatment for each child may vary.

The child and his or her caretaker(s) will be required to schedule office visits with the neurosurgeon for programming visits. For the first several months post-implantation, visits will occur every 2-4 weeks to monitor tolerability (Cyberonics, 2007), and each visit should take approximately 30 minutes (O'Reardon, et al. 2006).

Once a patient responds to VNS Therapy, no further changes are necessary and visits will be once every few months, as indicated by the neurosurgeon.

Outcome Assessment

Measures of the outcome of VNS therapy will be obtained from re-administration of the CBCL and TRF rating scales, as well as obtaining additional collections of salivary cortisol samples.

Both the rating scales and the biochemical samples will be obtained at intake, 6 months post-implantation, and 12 months post-implantation. The rationale for choosing the 6-month timeframe for both of the outcome measures is based on the reported timeframe of VNS effects, which occurs typically between 6 and 12 months (Mohr, et al. 2011). DSM-oriented scales will not be included in the outcome assessment, as they are not derived directly from problem scores obtained from standardized assessments of children (Achenbach & Rescorla, 2000; Achenbach & Rescorla, 2001).

With both the CBCL and TRF rating scales for the 1 ½-5 year old population, the criteria for inclusion is a clinically significant score (70+) on the following syndrome scales (there are a total of 7 syndrome scales):

1. Emotionally reactive
2. Anxious/depressed
3. Attention problems
4. Oppositional defiant problems

It is expected that by 6 or 12 months post-implantation, there may be changes in the results of the above syndrome scales. Specifically, that some of the scores may fall within the borderline range (65-69).

With both the CBCL and TRF rating scales for the 6-18 year old population, the criteria for inclusion is a clinically significant score (70+) on the following syndrome scales (there are a total of 8 syndrome scales):

1. Anxious/depressed
2. Social problems
3. Attention problems
4. Rule-breaking behaviors
5. Aggressive behaviors

It is expected that by 6 or 12 months post-implantation, there may be changes in the results of the above syndrome scales. Specifically, that some of the scores may fall within the borderline range (65-69).

It is acknowledged that different caretakers or teachers may have filled out the CBCL and TRF's during the initial evaluative process, and though this would be a confounding variable to the measurement, this research study is not within the confines of a controlled experiment, and thus will be taken into account.

With both the biochemical evaluation, the criteria for inclusion is that the child must have results, on average, that fall outside the higher end of the expected ranges for each child's age group. It is expected that by 6 or 12 months post-implantation, the average salivary cortisol range fall within normal limits for each child's age group.

The additional benefit of both the CBCL/TRF rating scales and the HS cortisol-kit are that both are relatively cost effective instruments to measure outcome; the HS cortisol kit is $260 for 38 tests (J.P, personal communication, May 21, 2014), and the CBCL and

TRF rating scales are $1 per rating form (University of Vermont, personal communication, May 21, 2014).

CHAPTER 5. IMPLEMENTATION, LIMITATIONS AND CONCLUSIONS

This chapter will provide a foundational base for the development of a program required to implement this type of study, and will also discuss current limitations, future research designs and conclusions.

Research and Evaluation Location

The location where the research team will be, and where each aspect of the evaluative process will take place, will be in an outpatient building attached to, and affiliated with, a large teaching hospital. The teaching hospital should have both psychiatric and neuropsychology units on either an inpatient or outpatient basis.

An overarching rationale for the research and evaluations of this study to be conducted at a teaching hospital is due to the productive research environment where care can be delivered to patients, and the fact that the various professionals can help train the next generation of professionals and conduct vital medical research.

Additionally, neurodevelopmental principles impact all child-related disciplines, and the fact is that the core concepts of neurodevelopment are rarely taught to trainees in psychiatry, psychology, pediatrics, social work, and medicine in general (Perry, 2009), and awareness of these concepts and experiences will hopefully be translated to the field and reinforce the interdisciplinary approach.

The Interdisciplinary Team

The interdisciplinary base of this study requires that professionals from five separate disciplines join together and form one cohesive and fluid team. These disciplines include a primary care physician, an LPC or LCSW clinician, a neuropsychologist, a PhD

level biochemist and a neurosurgeon; their functions are described in detail in the previous chapter.

Because the nature of this study requires a working knowledge of neural structure, organization and functioning, all team members must have experience and education within these areas. Additionally, all members of the team must be familiar with, and experienced in, child development, clinical traumatology, and developmental neurosciences in order to be contributing and effective members of the team. The team members will be selected based upon the above experiential and educational criteria.

Potential Funding Sources

Options for funding this study includes the Administration for Children and Families (ACS), the National Institute of Health (NIH), and/or Cyberonics, Inc, which is the manufacturer of the VNS device.

The Administration for Children and Families, which is a division of the Department of Health and Human Services, is responsible for federal programs that promote the economic and social well being of families, children, individuals and communities. The agency has a budget of more than $51 billion to assist in funding research, and for fiscal year 2014, 14% of that budget will go toward foster care and permanency research (ACF, 2014). The ACF partners with and selects certain state child welfare systems to implement the research. Benefits to this stakeholder include increasing numbers in achieving and maintaining permanency, retention of foster and adoptive parents, and ultimately the across-domain cost effectiveness within the child welfare

system in regard to overall mental health costs of children under their care and supervision.

The National Institute of Health is currently the largest federal funding agency of medical research (Association of American Medical Colleges [AAMC] , 2011), with the budget for fiscal year 2015 being $30.4 billion (NIH, 2014). The potential benefit to this stakeholder includes an improved quality of life for children with RAD as well as their caregiver(s), fiscal stability, and overall economic impact including global competitiveness (AAMC, 2011), and is in line with their mission to enhance health, lengthen life, and reduce illness and disability (NIH, 2014).

The manufacturer of the VNS device, Cyberonics, Inc., is also being recommended as a potential funding source as they have a commitment to supporting research endeavors, and provide investigator-initiated study grants for three general categories of research: clinical trials, animal trials, and device-only requests (Cyberonics, Inc., 2014). This study applies due to the fact that the VNS device and its prospective effects are the focus of this study. The potential benefits to this stakeholder includes increased use of the VNS device in the pediatric RAD population, and its potential effectiveness within this population would ultimately result in increased usage of the device overall, and spread of knowledge and education about the device and its potential application in a variety of other psychiatric disorders. The affiliation of the VNS device to the child welfare system and teaching hospital would also be a benefit, due to their combined large client and professional affiliations and the fact that they are already established agencies.

While the above are noted as benefits to the stakeholders, there are also risks, as with any investigative research study. Risks include the fact that VNS device having never being used for the treatment of RAD, the fact that VNS treatment has not been approved by the FDA or the American Academy of Child and Adolescent Psychiatry for use in this population, as well as the fact that there is a possibility that the outcomes of this study may not result in the desired outcomes. However, considering this device has been safely used and well tolerated in the pediatric epileptic population and has also shown effectiveness in treating mood and anxiety disorders, it is with confidence that the stakeholders will be inclined to participate and note the benefits over the risks. The additional long-term potential benefits of participating in this proposed research program would be having countless positive outcomes that would reverberate through many systems, from the greater community, down to each vulnerable child afflicted with RAD.

Limitations of the Current Study

Several limitations to this study should be mentioned and considered:

1. Lack of control group and randomization: Without a control group or randomization, one cannot draw definitive conclusions as to whether or not the outcomes were a direct result of the treatment itself or a placebo effect. The justification for lack of randomization and control group stems from the ethical standpoint that each child is equally suffering, and in need of prompt treatment.
2. Threats to external validity: Due to the heterogeneity of characteristics of participants (differences in ethnicity, gender, race, socioeconomic status, demographic differences, variations in treatment histories, child abuse/neglect

experiences, onset of age at the initial bond break and differences in socio-emotional functioning), error increases due to failure in specifying which characteristics interact with a cause-effect relationship. As a result, co-variation between treatment and outcomes will be obscured.

3. Threats to internal validity: The use of concomitant psychotropic medications and/or concurrent therapeutic interventions, and variations of these therapies within subjects, is cause for significant concern in regard to cause and effect. Rationale for allowing concurrent therapies include the fact that based upon the referral source, most participants referred will already be on medications and/or involved in some type of therapeutic intervention. The deleterious effects of titrating medications and/or discontinuing therapy with this population, could be deleterious not only to the child's well being, but also to achieving permanency within their respective foster or adoptive placement. An additional threat to internal validity includes the fact that these children will mature over time, and this maturation could be confused with a treatment effect.
4. Treatment resistance to psychotropic medication not required: For other device trials with VNS, treatment resistance to several rounds of psychotropic medications is typically required. The rationale for not requiring treatment resistance in this study is to minimize, as much as possible, the use of psychotropic mediations in children with RAD due to the fact that there its effects are systemic and not targeted, which results in a wide range of potential side

effects (Labar & Dean, 2002). The justification for this includes the ethical underpinnings of least intrusive intervention.

5. Results were not blinded: This concern arises from the fact that researchers, caregivers and the participants have an investment in the research with which they are conducting and participating in, and may also have expectations of success, which can potentially affect the results. Due to ethical reasons, in conjunction with the fact that this study is in includes a surgical intervention and also involves children, a single blind or double-blinded, placebo controlled strategy was not considered at this initial stage.
6. Threats to construct validity: Because the effects of VNS have been documented in individuals with mood disorders and anxiety, and children with RAD most likely will have similar and additional co-morbid diagnoses, the positive effects of VNS may not be a result of its effect on RAD, but may be due to its positive effects on the other co-morbid diagnoses.
7. Threats to inter-rater reliability: Inter-rater reliability with both the Teacher's Report Form (TRF) and Child Behavior Checklist (CBCL) may be low. One aspect of outcome measurement in this study includes both the TRF and CBCL checklist being filled out by the child's teacher(s) and caregiver(s) prior to commencing treatment, and then the checklist's being filled out at 6 and 12 months post-implantation. The issue presents itself after treatment has suspended, which is 6- 12 months post-implantation, and results in the reality that the child

may not have the same teacher(s) or caregiver(s) to fill out the TRF or CBCL at that time.

8. Potential variability of VNS stimulation parameters: Though there are specified stimulation parameters suggested in the literature for VNS in the pediatric population, parameters may vary considerably in practice. Without VNS parameters being consistent with each child, it is difficult to determine whether or not the outcomes were a confounding variable secondary to the differences in VNS stimulation parameters.
9. Conflict of interest: The conflict of interest within this study concerns the funding source, Cyberonics, Inc., as Cyberonics, Inc. is the manufacturer of the VNS device. This conflict adds the potential for bias due to their investment with the product.

Future research studies within this proposed research program should be designed, when possible, to limit the above limitations. It is recognized that the proposed population of this study is a vulnerable population as a result of their young age and accompanying potential safety and ethical issues, that specific limitations may be difficult to be avoided. On the other hand, there are a multitude of research designs and methods that could be proposed and still have a strong, empirically supported base while minimizing risk to each child and meeting ethical and moral provisions.

Future Research Designs

In order to follow the course of evidence based practice and contribute to the informed decision making processes of policymakers, future research designs of this

investigative research study are required to have minimal methodological flaws and be as robust as possible.

For the purposes of making clear recommendations for future research and study designs, different types of designs will be discussed in a hierarchal order, beginning with the least robust to the most robust. The purpose of this is to provide a structured manner in which future designs should proceed, in their naturally occurring, logical order, and serve as a template for the process of future research studies and designs.

Observational Studies: Cross-Sectional Studies

Observational studies are the first line studies that help provide a greater understanding of the process of behavioral change, and assists in generating hypotheses for further testing in rigorous evaluations (Grimshaw, Campbell, Eccles & Steen, 2000). These types of studies are beneficial as they are used to make inferences about possible relationships between one variable at one particular point in time.

Observational study options include cross-sectional designs, cohort studies, and case-control designs, and the chosen design requires that it is consistent with the research question and methodology. As a result, both cross-sectional study designs and cohort study designs are the only type of observational study that should be considered for this type of research study, as the research question and methodology are congruent with these designs.

Cross-sectional studies should be the first line designs considered for future research, as the cross-sectional design is the most appropriate for screening hypotheses, as it requires a relatively shorter time commitment and fewer resources to conduct

(Carlson & Morrison, 2009). Within this proposed research study, there are many hypotheses that are required to be screened through prior to discussing hypothetical research designs related to VNS therapy for RAD.

A crucial issue is that questions still remain about the conditions necessary for RAD to develop (Gleason, et al. 2011). Dimensions of parental behavior are complex and maltreatment can vary by levels of severity, types of maltreatment, and types of episodes (Baer & Martinez, 2006), and unfortunately, a reliable and valid system for defining, measuring, and classifying types of maltreatment has not yet been developed (Twardoz & Lutzker, 2010). Furthermore, it is common for children to experience multiple forms of maltreatment (Wilson, Hansen & Li, 2011), resulting in additional confounding complexities.

As a result, the first line of studies and hypotheses suggested for this proposed research program would need to be a screening through of various variables that are hypothesized to lead to a diagnosis of RAD, and to rule out experiential differences within the population that could have effects on attachment. This needs to be the first step in the study design process, in order to be able to focus in on a population that could be a potentially reliable, representative sample, for inclusion in a robust study where VNS therapy is used.

With cross-sectional designs the variables that can be evaluated are infinite; however, only a few options for future research hypotheses will be noted:

1) Null hypothesis: There will not be a difference between the age of initial bond rupture between child and primary caregiver(s) and a diagnosis of RAD.

Research hypothesis: There will be a difference between the age of initial bond rupture between child and primary caregiver(s) and a diagnosis of RAD.

2) Null hypothesis: There will not be a difference between the quantity of initial bond ruptures between child and primary caregiver(s) and a diagnosis of RAD. Research hypothesis: There will be a difference between the quantity of initial bond ruptures between child and primary caregiver(s) and a diagnosis of RAD.
3) Null hypothesis: There will not be a difference between the recidivism of out of home placements and a diagnosis of RAD. Research hypothesis: There will be a difference between the recidivism of out of home placements and a diagnosis of RAD.
4) Null hypothesis: there will not be a difference quantity of removals from the child's primary caregiver(s) and a RAD diagnosis. Research hypothesis: There will be a difference between quantity of removals from the child's primary caregiver(s) and a RAD diagnosis.

Sample sizes for these studies should be determined through consulting a statistician or methodologist, who would be able to calculate the adequate sample size for the respective study. It is imperative that the sample size is large enough to lead to conclusive and reliable results (Van der Tweel, 2014).

Subsequent to the state child welfare agency making referrals, the initial stage of data collecting would be conducted by the LCSW or LPC clinician by completing the biopsychosocial evaluation, CBCL and TRF rating scales, the DIPA, and obtaining cross-situational data from caregiver(s), school personnel, and/or other professionals. Behavior

and socio-emotional functioning will be cross-situationally assessed, in conjunction with a through review of history, and current differential diagnosis.

Once the biopsychosocial evaluation is complete, the clinician would have a team meeting with the primary researcher, the neuropsychologist and the biochemist will discuss whether or not that participant fits into their respective study requirements. The interdisciplinary team will decide criteria for inclusion in this study at the time of the experiment. At this stage in the process, the primary physician and the neurologist should not be included in this type of observational study, considering there are no treatment interventions taking place. In the event the participant does not meet criteria, that participant should be provided with an opportunity to be included in future research studies provided by this team, if applicable.

In the event the participant does meet the requirements to participate in the respective study, that participant would move forward with completing a neuropsychological evaluation concurrent to completing the biochemical evaluation. Differential diagnosis and potential neurobiological correlates of RAD symptoms will be obtained and validated through these measures.

Once all three of the evaluations are complete, the team members would then have a team meeting and render each participant as either appropriate or inappropriate for the study, depending upon whether they fit into the variables being studied, and then assign them to their respective groups. Because this would be an observational study, the participants would not be randomized.

Results of the study would be used to assess functionality of current hypotheses, to refine future hypotheses, and to be able to investigate these hypotheses in more robust research designs. Upon commencement of the cross-sectional study, the researchers should provide each participant's primary child welfare worker and caregiver(s) with the results of their evaluations and refer each participant to an appropriate treatment provider.

While observational studies can be useful, the limitations require that investigators be critically aware of these pitfalls and ensure that they are appropriately recognized and addressed (Carlson & Morrison, 2009). These limitations include significant problems with internal validity, rendering the results difficult to determine in regard to cause and effect.

Once various observational studies have been investigated and hypotheses have been more refined, the next step would be to move onto quasi-experimental designs.

Quasi-Experimental Designs: Pretest-Posttest Nonequivalent-Groups Design

There are many situations where randomization is not possible, and in these situations, the quasi-experimental design is available. In quasi-experimental designs, variables are controlled as much as possible to the point where the outcomes can be causally tied to the intervention (Shadish, Cook & Campbell, 2002) to the extent to which it can be assumed that other possible alternative hypotheses are implausible.

Quasi-experimental designs are a mid-point between observational study designs and randomized controlled trials, as they are stronger than observational studies, and weaker than RCT's. Though quasi-experimental designs are not the gold standard, they are not as lengthy or costly as RCT's (Reith, et al. 2013), and continue to be frequently

used in research. There are various quasi-experimental designs; some are considered quality designs while others are considered sub-par due to difficulties in interpretation. The most frequently used, quality, quasi-experimental design is the pretest-posttest nonequivalent-groups design (Lucasey, 2002; Morgan, Gliner & Harmon, 2000), and will be recommended as the first type of quasi-experimental design to be used for this study.

The pretest-posttest nonequivalent-groups design is comprised of first taking measurements on the groups prior to the intervention, then assigning participants to either the control or experimental group. A post-test is then done on both groups to determine whether there were any differences between the groups. For this investigative study, the structure of how this design could be conceptualized is below.

Subsequent to the state child welfare agency making referrals, the team members would follow all of the assessment steps in order, including medical evaluation and clearance, biopsychosocial evaluation, neuropsychological evaluation and concurrent biochemical evaluation. At the conclusion of the evaluative process, the team members would make a decision as to who would be viable participants to include in the study. Outcome measures for all participants will be the same, and include the CBCL and TRF rating scales and the biochemical evaluation. The interdisciplinary team will decide criteria for inclusion in this study at the time of the experiment.

It is important to acknowledge that this specific design is considered to be nonequivalent because it already takes into account the fact that there are characteristics between the groups that have not been measured that may interact with the treatment to cause differences between the two groups that may not be caused by the intervention

(Morgan, Gliner & Harmon, 2000). On the other hand, it is in the best interest of the researchers to take all threats to internal validity into account and control for, and limit the threats as much as possible, specifically in regard to the dependent variable.

For the purposes of ruling out any additional confounding variables and to make this research design as internally valid as possible, it would be in the best interest of the researchers to ensure that none of the participants are on any concomitant psychotropic medications, or receiving any type of therapeutic intervention.

On the other hand, the potential of being able to ascertain a substantial enough sample of children with RAD who are not receiving any type of treatment is limited. In the event there are participants available who are not receiving any type of treatment, the potential that they are higher functioning than those participants recruited who are already receiving treatment, results in another confounding variable that needs to be taken in to consideration, addressed, and controlled for.

In the event the researchers recruit participants who are already receiving treatment (medication and/or therapy), the researchers can consider titrating potential participants off of their medications and/or requiring the participants no longer attend their respective therapeutic interventions. This would then result in having to address a significant criticism of including the pediatric population in such research studies, which argues that the participant would be at an increased risk from not receiving active therapy, and is particularly suspect if an accepted treatment exists for a given condition (Flynn, 2003). Essentially, the researchers would have to determine which option would work the best for their study, and take all aspects of their decision into consideration. At

the end of the study, statistical control techniques might be taken into consideration as one method of controlling for extraneous variables where there were differences that could otherwise not be limited or controlled.

The question of sample sizes in pediatric studies is also a complex one due to the desire to reduce exposure of trial participants to any potential harm while balancing the need to obtain an adequate sample size to ensure the validity of trial results. Recommendations for good clinical practice in the design phase of a study with the pediatric population should be considered, and include utilizing previous information available from similar pediatric populations, use information from other adult or pediatric populations only when no previous information is available, and consulting with a statistician or methodologist about sample size calculation (Van der Tweel, 2014). It is recommended that in future studies, the recommendations for good clinical practice are adhered to, when it comes to sample size.

Once sample sizes are determined and participants have been cleared to participate in the study, the participants need to be separated into either the experimental or control group. An ethical dilemma in this process is determining which participant should receive the treatment in the initial study versus which participant should receive treatment as usual. The participants and their caregiver(s) will have already been informed via the established informed consent procedure informing them which group they will be a part of, and their decision to remain included in the study is a part of this process. Despite this, an ethical dilemma still exists. In order to satisfy this ethical dilemma, once the study is complete, the control group will have the opportunity to

receive VNS for the same amount of time the experimental group received VNS, which is 6 months, as that is the marker for which VNS effects may begin to appear (Mohr, et al. 2011).

The participants in the experimental group will all undergo surgery and implantation of the VNS device. Two weeks post-implantation, participants in the experimental group will have the VNS device turned on. The participants in the control group will receive treatment as usual. Posttest measures for participants in both groups should be at 6 months post-implantation and include salivary cortisol sampling, and re-administration of the CBCL and TRF rating scales. Criteria in regard to cut-off scores for the rating scales and expected salivary cortisol ranges will be decided by the interdisciplinary team at the time of the study.

This study should be implemented for at least 6 months, and no longer than 12, as 6 months that is the marker for which VNS effects may begin to appear and 12 months is when full effects are typically seen (Mohr, et al. 2011). Ethical reasons for the length of the study to be 6 months at a maximum include the fact that the control group is just as debilitated from their illness and at risk of not achieving permanency as the participants in the experimental group, and are entitled to an equal chance at rehabilitation.

While the pretest-posttest nonequivalent groups design is considered to be one of the higher quality types of quasi-experimental designs, this type of design's flaw is the lack of randomization. This results in a serious threat in selection bias because the groups may differ on some extraneous variables and not just differ on the levels of the independent variable.

In the future, the time series design quasi-experiment should be considered as an alternate or additional design, as it is the other high quality design (Morgan, Gliner & Harmon, 2000) within the quasi-experimental category.

Randomized Controlled Trials: A Two-Arm, Single-Blinded, RCT

The two-arm design is the simplest design used with random assignment (Grimshaw, Campbell, Eccles & Steen, 2000), and as a result is recommended as the first type of RCT design to be used for this study.

The two-arm design is comprised of at least two conditions, random assignment of units to conditions, and posttest assessment of conditions (Shadish, Cook & Campbell, 2002). Double blinding would result in a more robust design and is recommended for future RCT's; however, because there are limited research investigators participating in this study, double blinding is not possible at this point. For additional future studies, double blinding would make for a more robust trial. For this investigative study, the structure of how this design would be conceptualized is discussed below.

Subsequent to the state child welfare agency making referrals, the team members would randomly assign each participant to either the control (will not receive VNS stimulation) or experiment group (will receive VNS stimulation). For the purposes of ruling out any additional confounding variables, to make this RCT as internally valid as possible, it would be in the best interest of the researchers to ensure that none of the participants are on any concomitant psychotropic medications, or receiving any type of therapeutic intervention. The same ethical considerations in regard to this issue should be

taken into account with this RCT as discussed in the components of the quasi-experimental design study.

The question of sample sizes in this study should also follow the same recommendations for good clinical practice noted in the quasi-experimental design study, which includes utilizing previous information available from similar pediatric populations, using information from other adult or pediatric populations only when no previous information is available, and consulting with a statistician or methodologist about sample size calculation (Van der Tweel, 2014).

Upon being assigned to either the control or experiment group, each participant will undergo surgery and implantation of the VNS device. Two weeks post-implantation, participants in the experiment group will have the VNS device turned on. It has been established that most participants in VNS studies do not experience any sensations when the device is operated (Rush, et al, 2005) supporting the efficacy of this placebo-controlled design and the decision that participants in the control group will also be implanted, but not have the device turned on.

The fact that there is a placebo in this study poses an ethical issue that must be recognized and addressed. Currently, there are no guidelines for the ethical employment of placebo in research within the pediatric population; however, there are guidelines listed by the Committee on Drugs, which is a comparable equivalent, and should be considered and followed for this recommended RCT, as well as for future RCT's with this population.

Within the conditions, it is noted that placebos may be ethically employed in drug research in the pediatric population in the following circumstances: when there is no commonly accepted therapy for the condition and the agent under study is the first one that may modify the course of the disease process; when the commonly used therapy for the condition is of questionable efficacy; when the commonly used therapy for the condition carries with it a high frequency of undesirable side effects and the risks may be significantly greater than the benefits; when the placebo is used to identify incidence and severity of undesirable side effects produced by adding a new treatment of an established regimen; or when the disease process is characterized by frequent, spontaneous exacerbations and remissions and the efficacy of the therapy has not been demonstrated (Malhotra & Subodh, 2009).

A second ethical dilemma is determining which participant should receive the treatment in the initial study versus which participant should receive the placebo. Again, since this is a single-blind study, the participants will not know whether they are receiving stimulations; however, the participants and their caregiver(s) will have already been informed via the established informed consent procedure that there is a chance they may or may not be randomized to the placebo group. In order to satisfy this ethical dilemma, once the study is complete, the control group should receive VNS for the same amount of time the experimental group received VNS.

Posttest measures for both groups will be the same, and include salivary cortisol sampling, and re-administration of the CBCL and TRF rating scales at both 6 and 12 months post-implantation. Criteria in regard to cut-off scores for the rating scales and

expected salivary cortisol ranges will be decided by the interdisciplinary team at the time of the study.

This study should be implemented for 6-12 months, and should not be any longer than 12 months, as 6 months is the marker for which VNS effects may begin to appear (Mohr, et al. 2011) and 12 months is the reported timeframe for full effects to be observed. However, 12 months could be argued to be too long of a timeframe for ethical reasons. Ethical reasons include the fact that the control group is just as debilitated from their illness and at risk of not achieving permanency as the participants in the experimental group, and are entitled to an equal chance at rehabilitation. Future studies have the option to choose the timeframe, which they deem most appropriate for the nature of their study.

Even though this design would meet the gold standards of an RCT, there would still be limitations that would affect reliability and validity that would need to be taken into account. These include issues of inter-rater reliability as a result of potential differences in raters of the CBCL and TRF; issues of construct validity in regard to the potential the participants most likely present with co-morbid diagnoses; along with significant threats to external validity due to the heterogeneity of the participants.

While randomized trials have provided reliable assessments of the safety and efficacy of treatments that have produced substantial improvements in health, because of the large increases in cost and effort caused by the current regulatory systems, many existing and new interventions are not being evaluated (Reith, et al. 2013). This current issue presents a dilemma in regard to moving forward in constructing potential research

designs for this investigative study, because the purpose of this study is to not only provide an accessible and potentially efficacious treatment option to such a vulnerable population, but to also meet the rigors of the gold standard in research designs. As a result, future research designs for this study should strive to achieve the status of conducting RCT's; however, there should also be a focus on other types of research designs, as they are more accessible and cost-effective. The effects of VNS on RAD may be more likely to be evaluated within these designs, and there will most likely be less ethical barriers attached to them.

In the event future research designs include RCT's, the types of RCT's that should be investigated are those that are double-blinded once more investigators are recruited, randomized experiments with multiple treatments (varying VNS stimulation parameters), controls with pre-tests and post-tests, and longitudinal designs post the minimum 6 month time frame, and other single-arm or multiple-arm trials comparing the use of VNS with and without psychotropic medications, other concurrent therapies or other confounding heterogeneous variables.

Additional Suggestions

While there were only three proposed research designs discussed to minimize limitations and enhance robustness in future studies with VNS and RAD, there were several additional limitations discussed earlier that were not addressed within those proposed research designs. In order to address these, the following are suggestions as to how those limitations could possibly be addressed in future studies.

The heterogeneity of characteristics of the population in this current study is a significant threat to external validity, and is a concern and needs to be addressed in future studies. It is suggested that in future studies, the populations chosen be separated into homogenous groups such as by ethnicity, gender, race, socioeconomic status, demographic differences, variations in treatment histories, child abuse/neglect experiences, onset of age at the initial bond break and differences in socio-emotional functioning. Taking some of these differences into account will help decrease the error associated with cause-effect relationship.

The referral source recommended for all of the research designs discussed are from within the child welfare system, and ignores other subsets of children with RAD who are as equally in need. Future research designs should consider having alternate referral sources, which would provide access to children who have RAD outside of the foster care and child welfare system.

The population being recommended for all of the research designs discussed are children between 5-7 who are in foster care, in the custody of child welfare, and whose biological parents have had their parental rights terminated. Future studies should consider including children whose parents rights are not terminated, in a concerted effort to maintain permanency within the home of the biological parent.

The variability of stimulation parameters that may occur within studies using VNS therapy is another concern. While there are recommended stimulation parameters for within this age group and this study, tolerability and effects may be different for each participant, resulting in the neurosurgeon possibly having to make unique modifications

to one participant's parameters versus another. In the event all stimulation parameters are not the same, this results in an increase of error associated with the cost-effect relationship. In an effort to maintain reliability, it is suggested that when a participant requires different stimulation parameters that they be excluded from the study while continuing to receive treatment for the length of the proposed study. This would fulfill ethical requirements while simultaneously enhancing reliability.

Double blinding should be considered in future research designs to reduce bias and increase robustness. In one of the research designs discussed earlier, single blinding (blinding of the participants) was recommended, and double blinding was not due to ethical and safety concerns in conjunction with having limited research staff. The safety issue entails having all researchers blinded. What would be a feasible, though not a cost-effective solution to this problem, would be to hire an independent neurosurgeon who has no conflict of interest in the study to be the neurosurgeon who conducts all post-implantation procedures and follow up appointments.

The last limitation pertains to outcome measures with the CBCL and TRF rating scales, and the concern of the threat to inter-rater reliability. The issue presents itself after treatment has suspended, which is 6- 12 months post-implantation, and results in the reality that the child may not have the same teacher(s) or caregiver(s) to fill out the TRF or CBCL at that time. In an effort to decrease the chances of this occurring with the TRF in future studies, the researchers could ensure the beginning of VNS stimulation begins only at the beginning of the school year, which would give enough time to do a 6-12 month study; therefore, increasing inter-rater reliability for the TRF. In regard to the

CBCL, it is known that foster placements can be unpredictable, and because of this reality, this may continue to be a limitation in future research studies.

Overall, most of these limitations can be adequately addressed in future research studies, resulting in minimal methodological flaws.

Conclusions

RAD is only one of the many possible psychological consequences of early childhood maltreatment (Hornor, 2008), and predicts negative affective, somatic and behavioral outcomes both in childhood and adulthood in a linear fashion (Johnson-Reid, Kohl & Drake, 2012). Though there are no prevalence estimates for children in foster or adoptive care with RAD, there is a high prevalence of behavior problems found among foster children who have experienced abuse and/or neglect, which have significant negative impact on foster children's placement and permanency outcomes (Leathers, Spielfogel, Gleeson & Rolock, 2012). To date, there are no current empirically supported treatments for RAD (Boekamp, 2008; O'Connor & Zeanah, 2003), and there are no current psychopharmacological treatments indicated for RAD (NIMH, 2012).

Psychopharmacological treatments that are used for children with RAD are prescribed on an off label basis (Bonati & Clavenna, 2005) having little or no sound scientific evidence for the condition which the medication is treating. Even more detrimental are the difficulties that arise in the form of medication side effects which occur because systemically administered psychotropics are transported via cerebral circulation, they cross the blood-brain barrier, and in turn effect neuronal excitation and inhibition in areas of normal brain function (Labar & Dean, 2002).

All of these aforementioned issues add to the complexities of the treatment paradigms and potential deleterious outcomes for these children, and the broader society and systems in general.

In an effort to develop an evidence-based treatment for RAD, VNS has been reviewed and considered for further study as a potentially efficacious treatment intervention for children 5-7 years of age with this disorder. Despite the fact that there is an obvious need for further research in this area, there is obligation as a scientific community, and to the larger community at hand, to not only focus on treating the symptoms, but to understand the etiology of the neurobiological aspects of this disorder and move toward more effective, regionally targeted, scientifically based interventions with the least amount of deleterious side effects.

Rationale for recommending 5-7 years of age as the range for this intervention includes the fact that seven years and younger is when neural plasticity is highly accessible (Delima & Vimpani, 2011; Perry, 2009; Johnson, 2009), and the brain around this time is also at a heightened state of vulnerability (Heim & Binder, 2011). Additionally, the mean age for which children are adopted in the U.S is 6.4 (U.S Children's Bureau, 2013), and RAD symptoms begin before age 5 (APA, 2000).

VNS is postulated to have projective effects on limbic system structures, in conjunction with direct effects on specific neurotransmitter systems involved in anxiety (norepinephrine) and mood modulation (serotonin)(George, Rush, Sackeim & Marangell, 2003; Conway, et al. 2012). Additionally, VNS has the ability to excite or inhibit neuronal activity, thus affecting the neurotransmitter concentration in different regions of

the brain (Albert, et al. 2009). These putative mechanisms of action would have direct effects on specific regions of the brain and neurotransmitters that are directly implicated in the neurobiology of RAD.

Of similar importance is the fact that the effects of VNS are not systemic in nature, as they are systemic in psychopharmacological treatments. With VNS, only the brain correlates associated with RAD will be targeted and treated, avoiding the systemic problems seen in psychotropic medications all together. Other benefits include a limited amount of office visits and diminutive length of treatment time in comparison to traditional psychiatric treatments (O'Reardon, et al. 2006), contributing to the cost-effectiveness of this treatment, and the fact that VNS provides the minimum level of invasiveness in comparison to alternative brain stimulation techniques (Malhi & Sachdev, 2007).

Adding to the rationale for the use of VNS in the RAD population is the observation that patients treated with VNS for epilepsy experienced mood improvement and quality of life improvement, and also experienced anxiolytic effects (Fitzgerald, 2011). Subsequent studies in the psychiatric population revealed similar results. Safety and tolerability of VNS for the treatment of refractory epilepsy in the pediatric population has been established (Morris III, et al., 2013; Awaad, Rizk, Roosen, Mcintosh & Waines, 2011), and these studies provide a strong base for the potential safety and tolerability of VNS in the RAD pediatric population.

This is the first recommendation of its kind, and is based upon a fusion of empirical evidence drawn from literature in the areas of developmental psychology,

psychiatry, medicine, and neuroscience. Notwithstanding the above supportive evidence for the use of VNS in RAD, the potential relevance of VNS in the treatment of RAD remains to be determined, as there have been no such studies implicating VNS and RAD. The potential usefulness of VNS in treating RAD deserves further exploration, and it is with optimism prudency that this applied theoretical model will come to fruition in the form of investigative research designs, as treatment options for RAD are urgently needed.

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APPENDIX A. MEDICAL EXAM FORMAT

From: "*Neuroanatomy Through Clinical Cases*, Second Edition", by Blumenfeld, 2010, Yale University School of Medicine, Sinauer Associates, Inc. Publishers. Sunderland, Massachusetts, 5-7.

1. Chief complaint
    - A succinct statement that includes the patient's age, sex, and presenting problem. It may also include one or two very brief pieces of pertinent historical data
2. History of present illness
    - This is the complete history of any current medical problem, including any possible risk factors or other causes of the current illness as well as a detailed chronological description of all symptoms and prior care obtained fort his problem. Pertinent negative information (symptoms or problems that are not present) helps exclude alternative diagnoses and is as important as pertinent positive information. Related medical problems can be mentioned as well; however, those that are not directly relevant to the present illness are usually covered instead in the section on past medical history
3. Past medical history
    - Prior medical and surgical problems not directly related to the history of present illness are described here
4. Review of systems:
    - A brief, head to toe review of all medical systems and diseases should be perused to pick up problems or complaints missed in earlier parts of the history. If something comes up that is relevant to the history of present illness, it should be inserted into the history of present illness section
        a. Head
        b. Eyes
        c. Ears
        d. Nose and throat
        e. Pulmonary
        f. Cardiac
        g. Gastrointestinal
        h. Genitourinary
        i. OB/GYN
        j. Dermatologic
        k. Neurologic
        l. Psychiatric
        m. Musculosekeletal
        n. Hematological
        o. Oncologic
        p. Rheumatological

q. Endocrine
r. Infectious

5. Family history
    - This section should include a list of all immediate family members and note familial illnesses such as diabetes, hypertension, asthma, heart disease, cancer, depression, and so on, especially those relating to the history of present illness. Family tree format is often a succinct and clear way to present this data
6. Social environmental history
    - This section should include the patient's family situation, travel history, sexual history
7. Medications and allergies:
    - This section should include a list of all medications currently being taken by the patient, including herbal or over the counter drugs, as well as any known general drug allergies
8. Physical exam:
    - The examination generally proceeds from head to toe and includes the following sections:
        a. General appearance
        b. Vital signs
        c. Head, eyes, ears, nose and throat
        d. Back and spine
        e. Lymph nodes
        f. Breasts
        g. Lungs
        h. Heart
        i. Abdomen
        j. Extremities
        k. Pulses
        l. Rectal
        m. Pelvic and genitalia
        n. Dermatologic
9. Laboratory Data:
    - Blood work
    - Urinalysis
10. Assessment and plan
    - Assessment: Begins with a one or two-sentence summary, or formulation that encapsulates the patient's main clinical features and most likely diagnosis. In more diagnostically uncertain cases, a brief discussion is added to the assessment, including a differential diagnosis, that is a list of alternative possible diagnoses.

- Plan: Immediately follows the assessment section and is usually broken down into a list of problems and proposed interventions and diagnostic procedures

APPENDIX B. SEMI-STRUCTURED BIOPSYCHOSOCIAL EVALUATION TEMPLATE

From: "*Synopsis of Psychiatry: Behavioral Sciences/Clinical Psychiatry*, Tenth Edition", by Sadock, J., & Sadock, V., 2007, Lippincott Williams & Wilkins, a Kluwer Business, 238-241.

I. Psychiatric History
   A. Identification: Name, age, sex, language if other than English, race, nationality, and religion; with whom the patient lives
   B. Chief complaint: Exactly why the patient the child's caretaker(s) and child welfare worker are requesting evaluation for potential VNS therapy
   C. History of present illness: Chronological background and development of the symptoms or behavioral changes that culminated in the caretaker(s) and child welfare worker seeking assistance; child's life circumstances at the time of onset; personality when well; how illness has affected life activities and personal relations- changes in personality, interests, mood, attitude toward others; dress, habits, level of tenseness, irritability, activity, attention, concentration, memory, speech; psychophysiological symptoms- nature and details of dysfunction; how anxieties are handled- avoidance, repetition of feared situation, what activities alleviate these fears/anxieties
   D. Past psychiatric and medical history: 1) Emotional or mental disturbances- extent of incapacity, type of treatment, names of hospitals, length of illness, effect of treatment; 2) Psychosomatic disorders- headaches, colitis, recurrent colds, skin conditions; 3) Medical problems
   E. Family history: Ethnic, national and religious traditions; other persons in the home and descriptions of them- personality and intelligence- and what has become of them; descriptions of different households lived in (including all information about ethnicity, descriptions of those individuals, what has become of them, etc); present relationships between the child and those who were and are in the family; role of illness in the family; family history of mental illness; where does the child currently live- neighborhood and particular residence of the child; is the home crowded; privacy of family members from each other and from other families; source of family income and difficulties in obtaining it; public assistance and attitude about it; who is the primary caretaker
   F. Personal history: history of the child's life from infancy to the present (chronological order); emotions and/or behaviors associated with different life periods (painful, stressful, conflictual)
      1. Early childhood (Birth through age 3)

a. Prenatal history and mothers pregnancy and delivery: length of pregnancy, spontaneity and normality of delivery, birth trauma, whether child was planned and wanted, birth deficits
b. Feeding habits: Breast-fed or bottle-fed, eating problems
c. Early development: Maternal deprivation, language development, motor development, signs of unmet needs, sleep patterns, object constancy, stranger anxiety, separation anxiety
d. Toilet training: age, attitude of parents, feelings about it
e. Symptoms of behavior problems: Thumb sucking, temper tantrums, head bumping, rocking, night terrors, fears, bed-wetting or bed soiling, nail biting, masturbation
f. Personality and temperament as a child: Shy, restless, overactive, withdrawn, studious, outgoing, timid, athletic, friendly, patterns of play, relations to siblings

2. Middle childhood (ages 3 to 11): Early school history- feelings about going to school, early adjustment, gender identification, conscience development, punishment; social relationships, attitudes toward siblings and playmates

II. Mental Status

A. Appearance

1. Personal identification: May include a brief nontechnical description of the child's appearance and behavior as a novelist might write it; attitude toward examiner can be described- cooperative, attentive, interested, frank, seductive, defensive, hostile, playful, ingratiating, evasive, guarded
2. Behavior and psychomotor activity: Gait, mannerisms, tics, gestures, twitches, stereotypes, picking, touching examiner, echopraxia, clumsy, agile, limp, rigid, retarded, hyperactive, agitated, combative, waxy. Interactions with caregiver(s)
3. General description: Posture, bearing, clothes, grooming, hair, nails, healthy, sickly, angry, frightened, apathetic, perplexed, contemptuous, ill at ease, poised, old looking, young looking, effeminate, masculine; signs of anxiety- moist hands, perspiring forehead, restlessness, tense posture, strained voice, wide eyes, shifts in anxiety during interview or with particular topic

B. Speech: Rapid, slow, pressured, hesitant, emotional, monotonous, loud, whispered, slurred, mumbled, stuttering, echolalia, intensity, pitch, ease, spontaneity, productivity, manner, reaction time, vocabulary, prosody

C. Mood and affect

1. Mood: How does the child say he or she feels; depth, intensity, duration and fluctuations of mood- depressed, despairing,

irritable, anxious, terrified, angry, expansive, euphoric, empty, guilty, awed, futile, self-contemptuous, anhedonic, alexithymic

2. Affect: How examiner evaluates the child's affect- broad, restricted, blunted or flat, shallow, amount and range of expression; difficulty in initiating, sustaining or terminating an emotional response; is the emotional expression appropriate to the thought content, culture, and setting of the examination; give examples if emotional expression is not appropriate

D. Thinking and perception
    1. Form of thinking
        a. Productivity: Overabundance of ideas, paucity of ideas, rapid thinking, slow thinking, hesitant thinking; does the child speak spontaneously or only when questions are asked, stream of thought, quotations from the child
        b. Continuity of thought: Goal directed, relevant or irrelevant; loose associations; illogical, tangential, circumstantial, rambling, evasive, perseverative statements, blocking or distractibility
        c. Language impairments: Incoherent or incomprehensible speech, clang associations, neologisms
    2. Content of thinking
        a. Preoccupations: about the illness, environmental problems; obsessions, compulsions, phobias; obsessions or plans about suicide, homicide; hypochondriacal symptoms, specific antisocial urges or impulses
    3. Thought disturbances
        a. Delusions: Content of any delusional system, its organization, the patient's convictions as to its validity, how it affects his or her life: persecutory delusions- isolated or associated with pervasive suspiciousness; mood-congruent or mood-incongruent
        b. Ideas of reference and ideas of influence: How ideas began, their content, and the meaning the patient attributes to them
    4. Perceptual disturbances
        a. Hallucinations and illusions: Whether the child hear voices or sees visions; content, sensory system involvement, circumstances of the occurrence; hypnagogic or hypnopompic hallucinations; thought broadcasting
        b. Depersonalization and derealization: Extreme feelings of detachment from self or from the environment
    5. Dreams and fantasies
        a. Dreams: Prominent ones, if patient will tell them; nightmares

b. Recurrent, favorite, or unshakable daydreams

E. Sensorium
   1. Alertness: Awareness of environment, attention span, clouding of consciousness, fluctuations in levels of awareness, somnolence, stupor, lethargy, fugue state, coma
   2. Orientation
      a. Time: Whether the child identifies the day correctly; or approximate date; time of day, behaves as though oriented to the present
      b. Place: Whether the child knows where he or she is
      c. Person: Whether the child knows who the examiner is, and the roles or names of the persons with whom in contact
   3. Concentration: Whether anxiety or some disturbance of mood or concentration seems to be responsible for difficulty
   4. Memory: Impairment, efforts made to cope with impairment-denial, confabulation, catastrophic reaction, circumstantiality used to conceal deficit: whether the process of registration, retention, or recollection of material is involved
      a. Remote memory: Childhood data, important events known to have occurred when the patient was younger or free of illness, personal matters, neutral material
      b. Recent past memory: Past few months
      c. Recent memory: Past few days, what did patient do yesterday, the day before, have for breakfast, lunch, dinner
      d. Immediate retention and recall: Ability to repeat six figures after the examiner dictates them- first forward, then backward, then after a few minutes interruption (if developmentally appropriate)
      e. Effect of defect on child: Mechanisms patient has developed to cope with defect

F. Insight: Degree of personal awareness and understanding of illness
   1. Complete denial of illness
   2. Slight awareness of being sick and needing help but denying it at the same time
   3. Awareness of being sick but blaming it on others, on external factors, on medical or unknown organic factors
   4. Intellectual insight: Admission of illness and recognition that symptoms or failures in social adjustment are due to irrational feelings or disturbances, without applying that knowledge to future experiences
   5. True emotional insight: Emotional awareness of the motives and feelings within, of the underling meaning of symptoms; does the awareness lead to changes in personality and future behavior;

openness to new ideas and concepts about the self and the important persons in his or her life

G. Judgment
    1. Social judgment: Stable manifestations of behavior that are harmful to the child and contrary to acceptable behavior in the culture; does the child understand the likely outcome of personal behavior and is the child influenced by that understanding; examples of impairment
    2. Test judgment: Child's prediction of what he or she would do in imaginary situations

From: "*Clinical Social Work Practice: An Integrated Approach*, Second Edition", by Cooper, M., & Lesser, J., 2005, Pearson, 53.

III. Summary of Findings
IV. Diagnosis (DSM-IV-TR)
V. Summary
VI. Recommendations and goals for treatment

APPENDIX C. TEACHERS REPORTING FORM AND CHILD BEHAVIOR CHECKLIST AGES 6-18 PSYCHOMETRIC PROPERTIES

From: "*Manual for the ASEBA School-Age Forms and Profiles. An Integrated System of Multi-Informant Assessment*", by Achenbach, T., & Rescorla, L., 2001, Burlington, VT: University of Vermont, Research Center for Children, Youth & Families, 1-135.

Both the Teachers Reporting Form (TRF) and the Caregiver Behavior Checklist (CBCL) enables users to quickly obtain standardized ratings, and descriptive details of children's functioning.

Teachers and other school personnel who are familiar with the child's functioning in school, such as teacher aides, counselors, administrators, and special education educators, should complete the TRF. Parents, parent surrogates and caregivers should complete the CBCL.

The format consists of 138 questions including open-ended items that ask the respondent what concerns them most about the child, and the best things about the child. The form can typically be completed in about 15-20 minutes. Both the TRF and CBCL include empirically based syndrome scales and DSM-oriented scales. The DSM oriented diagnostic scales are not derived directly from problem scores obtained from standardized assessments of children, while the CBCL syndrome scales are.

Items for both the CBCL and TRF empirically based syndrome scales are designated as anxious/depressed; withdrawn/depressed; somatic complaints; social problems; thought problems; attention problems; rule-breaking behaviors and aggressive behaviors. The DSM- oriented scales are designated as affective problems, anxiety problems, somatic problems, ADD/HD problems, oppositional defiant problems and conduct problems.

T-scores between 65-69 are considered borderline and scores of 70+ are considered clinical. The score ranges for the DSM-oriented scales are the same. Scores in the borderline and clinical ranges significantly discriminate between children who are referred for mental health or special education services for behavioral/emotional problems and children who are not referred.

Normative Data

Normative data was obtained through Temple University's Institute for Survey Research through using their national sampling frame between February 1999 and January 2000. The norms are designed for ages 6-18.

Based on CBCL responses, 1, 753 samples provided the norms for the CBCL scales and based on the TRF responses, 2, 319 samples provided the norms for the TRF scales.

Demographics for the CBCL scales are as follows: 52% boys, 48% girls; 33% upper class, 51% middle class, 16% lower class; 60% non Latino white, 20% African American, 9% Latino, 12% mixed or other; 17% from the Northeast region of the U.S, 20% from the Midwest, 40% from the South, and 24% from the West.

Demographics for the TRF scales are as follows: 48% boys, 52% girls; 38% upper class, 46% middle class, 16% lower class; 72% non Latino white, 14% African American, 7% Latino, 7% mixed or other; 19% from the Northeast region of the U.S, 23% from the Midwest, 26% from the South, and 23% from the West.

Reliability and Validity

To assess inter-interviewer reliability of item scores, scores that were obtained by three interviewers on 241 matched trials of children (for a total sample of 723 children) were compared. The overall inter-interviewer reliability was .93 for the 20 competence items and .96 for the 118 specific problem items ($p<.001$). This indicates very high inter-interviewer reliability in scores obtained for each item relative to scores obtained for each other item.

Test-retest item reliabilities were computed from CBCL's obtained by a single interviewer who visited mothers of 72 non-referred children at a 1-week interval. The overall inter-interviewer reliability was 1.00 for the 20 competence items and .95 for the 118 specific problem items (both $p<.001$). This indicates very high test-retest reliability in scores obtained for each other item.

Syndrome scales were derived from factor analyses of the correlations among all items. The composition of the scales is therefore based on internal consistencies among certain subsets of items. The alphas for the competence scales were moderately high, ranging from .63 to .79 for the CBCL. Alphas were not shown for the TRF adaptive characteristics because each one has only a single score, nor for Academic Performance, which may comprise only one score when teachers rate performance in a single subject. Alpha was .90 on the TRF Total Adaptive scale. For the empirically based problem scales, the alphas ranged from .78 to .97 on the CBCL and .72 to .95 on the TRF. For the DSM-oriented scales, alphas ranged from .72 to .91 on the CBCL and .73 to 94 on the TRF.

Regarding content validity of the CBCL and TRF, items have been strongly supported by nearly four decades of research, consultation, feedback, and refinement, as well as by the current evidence for the ability of all the items to discriminate significantly ($p<.01$) between demographically similar referred and non-referred children. For both the

CBCL and TRF, pairs of referred and non-referred children were selected and identified in gender and age, and were as similar as possible in socioeconomic status and ethnicity.

The criterion-related validity of the CBCL and the TRF scales were supported by multiple regressions, odds ratios, and discriminant analyses, all of which showed significant (p<.01) discrimination between referred and non-referred children.

APPENDIX D. TEACHERS REPORTING FORM AND CAREGIVER BEHAVIOR CHECKLIST AGES 1 ½ -5 PSYCHOMETRIC PROPERTIES

Both the Teachers Reporting Form (TRF) and the Caregiver Behavior Checklist (CBCL) enables users to quickly obtain standardized ratings, and descriptive details of children's functioning. Parents, parent surrogates and caregivers should complete the CBCL, while preschool teachers and other school personnel should complete the TRF.

With the TRF, staff members who have had the most experience with the child over the longest period of time (for a minimum of 2 months) should be completing the forms, and their responses should be based on the child's behavior within the past 2 months. Because there may be different staff members experiencing the child in different settings, it would be suitable to have as many daycare or preschool staff as possible to complete separate TRF forms on each child. With the CBCL, both caregivers are able to complete separate forms on each child as well. (Furlong, n.d).

The format consists of a total of 99 questions including open-ended items that ask the respondent what concerns them most about the child, and the best things about the child. The forms can typically be completed in about 15-20 minutes. Both the TRF and CBCL include empirically based syndrome scales and DSM-oriented scales. The DSM oriented diagnostic scales are not derived directly from problem scores obtained from standardized assessments of children, while the CBCL syndrome scales are (Achenbach & Rescorla, 2000).

Items for the TRF empirically based syndrome scales are designated as emotionally reactive, anxious/depressed, somatic complaints, withdrawn, attention problems and oppositional defiant problems. The CBCL empirically based syndrome scales are the same; however, there in one additional scale- the sleep problems scale. DSM-oriented scales are designated as affective problems, anxiety problems, pervasive developmental problems, attention deficit/hyperactivity problems and oppositional defiant problems T-scores between 65-69 are considered borderline and scores of 70+ are considered clinical. The score ranges for the DSM-oriented scales are the same. Scores in the borderline and clinical ranges significantly discriminate between children who are referred for mental health or special education services for behavioral/emotional problems and children who are not referred (Achenbach & Rescorla, 2000).

Normative Data

Normative data was obtained through Temple University's Institute for Survey Research through using their national sampling frame between February 1999 and January 2000. The norms are designed for ages 1 ½-5 years old. Based on CBCL responses, 700 samples provided the norms for the CBCL scales and based on TRF

responses, 1,192 samples provided the norms for the TRF scales (Achenbach & Rescorla, 2000).

Demographics for the CBCL scales are as follows: 33% upper class, 49% middle class, 17% lower class; 56% non Latino white, 21% African American, 13% Latino; 10% mixed or other; 17% from the Northeast region of the U.S, 22% from the Midwest, 40% from the South, and 21% from the West.

Demographics for the TRF scales are as follows: 47% upper class, 43% middle class, 10% lower class; 48% non Latino white, 36% African American, 8% Latino, 9% mixed or other; 29% Northeast region of the U.S, 17% from the Midwest, 32% from the South, and 22% from the West.

Reliability and Validity

To assess reliability in both the rank order and magnitude of scale scores, test-retest Pearson correlations (*r*s) and *t* tests of differences between mother's CBCL ratings of 68 non referred children on two occasions, at a mean interval of 8 days, were scored. Reliability was high for most scales, with most test-retest *r*s being in the .80s and .90's. The Total Problems *r* was .90 on the CBCL and .88 on the TRF. Across all scales, the mean *r* was .85 on the CBCL and .81 on the TRF (Achenbach & Rescorla, 2000).

The commonly found tendency for problem scores to decline over brief rating intervals was evident in the scale scores, but it accounted for a mean of only 0.9% of the variance in the CBCL scores and 1% in the TRF scores.

CBCL stability correlations averaged .61 over a 12-month period, while TRF correlations averaged .59 over a 3-month period. Nearly all of the items discriminated significantly ($p \leq .01$) between referred and non referred children and/or were assigned to empirically based or DSM-oriented scales. The criterion related validity of the problem scales was supported by significant discrimination between referred and non-referred children. The construct validity of the problem scales was supported by concurrent and predictive associations with a variety of other measures, plus evidence for substantial genetic components of the patterns of problems assessed by the scales (Achenbach & Rescorla, 2000).

APPENDIX E. DIAGNOSTIC INFANT AND PRESCHOOL ASSESSMENT (DIPA) PSYCHOMETRIC PROPERTIES

The Diagnostic Infant and Preschool Assessment interview was created specifically for parents of infants and preschoolers 1-6 years of age. Interviews take between 45 and 90 minutes to complete, and are scored manually.

The psychometric properties of the DIPA are based upon caregivers of 50 outpatients aged 1-6 years who were interviewed twice by trained interviewers, once by a clinician and once by a research assistant. The median test-retest intra-class correlation was 0.69, mean 0.61, and values ranged from 0.24-0.87. The median test-retest kappa was 0.53, mean 0.52, and values ranged from 0.38 to 0.66. There were no differences by duration between interviews (De Young, Kenardy & Cobham, 2011; Gleason, et al. 2010; De Young, Kenardy, Cobham & Kimble, 2012).

Concurrent criterion validity showed good agreement between the instrument and DSM-based CBCL scales when the DSM-based scales were matched well to the disorder. Overall, preliminary data support the DIPA as a reliable and valid measure of symptoms in research and clinical work with very young children (Scheeringa & Haslett, 2010).

The diagnoses in the DIPA are based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR), and the Research Diagnostic Criteria: Preschool Age (RDC: PA), which includes empirically validated, developmentally sensitive modifications to diagnostic criteria. When scoring, the DIPA tally sheet provides instructions to apply either the DSM-IV-TR or the RDC:PA criteria in making a diagnosis (Gleason, Zeanah & Dickstein, 2010).

The DIPA has been used in a total of three studies by (De Young, Kenardy & Cobham, 2011; Gleason, et al. 2010; De Young, Kenardy, Cobham & Kimble, 2012).

APPENDIX F. DEVELOPMENTAL NEUROPSYCHOLOGICAL ASSESSMENT BATTERY-II (NEPSY-II) PSYCHOMETRIC PROPERTIES

The NEPSY-II is a comprehensive neuropsychological battery of children ages 3-12 years that includes 32 subtests divided into 6 content domains.

The 6 domains and associated 32 subtests are as follows (Harcourt Assessments, 2007):

1) Attention and Executive Functioning: animal sorting; auditory attention and response set; clocks; design fluency; inhibition, and statue
2) Language: body part naming; comprehension of instructions; oromotor sequences; phonological processing; repetition of nonsense words; speeded naming, and word generation
3) Memory and Learning: list memory and list memory delayed; memory for designs and memory for designs delayed; memory for faces and memory for faces delayed; memory for names and memory for names delayed; narrative memory; sentence repetition, and word list interference
4) Sensorimotor: fingertip tapping; imitating hand positions; manual motor sequences, and visuomotor precision
5) Social Perception: affect recognition and theory of mind
6) Visuospatial Processing: arrows, block construction; design copying; geometric puzzles; picture puzzles, and route finding

The NEPSY-II normative sample is a national, stratified random sample consisting of 1, 200 preschoolers, children and adolescents between the ages of 3 and 16 years old, collected between 2005 and 2006. There were 100 children (50 boys, and 50 girls) in each of the 12 age groups: 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13-14, and 15-16 years of age. For ages 3 to 12 years, each age group contained 50 children in the first six months and 50 children in the second six months of the year. Stratification by age, race/ethnicity, geographic location, and parental education was based on the October 2003 United States census survey. Exclusion criteria included diagnosis of a number of conditions that could potentially affect scores, including neurological, learning, sensory/motor and psychiatric disorders, recent history of previous testing, and medication usage that might potentially impact performance (Brooks, et al. 2010).

In order to assess the clinical and diagnostic utility of the NEPSY-II, 10 special group studies were conducted during the standardization, and included children with the following diagnoses: ADHD, autistic disorder, aspergers disorder, deaf and hard of hearing, emotionally disturbed, language disorder, mild intellectual disability, mathematics disorder, reading disorder and traumatic disorder (Kemp & Korkman, 2010).

Strong evidence of convergent and discriminant validity is provided by correlational studies with the following instruments: NEPSY, Wechsler Intelligence Scale for Children

(WISC-IV), Differential Abilities Scales- Second Edition (DAS-II), Wechsler Nonverbal Scale of Ability (WNV), Wechsler Individual Achievement Test- Second Edition (WIAT-II), Children's Memory Scale (CMS), Delis-Kaplan Executive Function System (D-KEFS), Bracken Basic Concept Scale-Third Edition: Receptive (BBCS-3:R), Bracken Basic Concept Scale-Expressive (BBCS:E), Deveraux Scales of Mental Disorders (DSMD), Children's Communication Checklist-Second Edition, United States Edition (CCC-2), Brown Attention-Deficit Disorder Scales for Children and Adolescents (Brown ADD Scales), and Adaptive Behavior Assessment System-Second Edition (ABAS-II) (Harcourt Assessments, 2007).

Inter-rater reliability for the NEPSY-II was calculated as percent agreement rates between trained scorers for subtests. They ranged from 93-99%.

The NEPSY-II manual presents a voluminous amount of information on subtest reliability co-efficents, separated by age groups (Kemp & Korkman, 2010).

For 5-6 year olds reliability co-efficents are as follows: Inhibition naming total completion time .94; inhibition total completion time .80; comprehension of instructions .83; phonological processing total score .92; memory designs for content score .77; memory designs for spatial score .96; memory design total score .95; sentence repetition total score .96; affect recognition total score .90; theory of mind total score .85; arrows total score .92; block construction total score .94; design copying motor score .89; design copying global score .78; design copying local score .77; and design copying total .91 (Harcourt Assessments, 2007).

For 7-12 year olds reliability co-efficents are as follows: Clocks total score .88; inhibition naming total completion time .84; inhibition total completion time .80; inhibition switching total completion time .86; comprehension of instructions total .80; phonological processing total score .90; memory for designs content score .86; memory for designs spatial score .88; memory designs total score .93; word interference repetition score .80; word interference recall total score .67; affect recognition total score .88; block construction total score .85; arrows total score .92; design copying motor score .74; design copying global score .73; design copying local score .74; design copying total score .88; geometric puzzle .82; and picture puzzle total score of .89 (Harcourt Assessments, 2007).

APPENDIX G. ABBREVIATED NEUROLOGIC EXAM PROCEDURE

From: "*Neuroanatomy Through Clinical Cases*, Second Edition", by Blumenfeld, 2010, Yale University School of Medicine, Sinauer Associates, Inc. Publishers. Sunderland, Massachusetts, 81.

PART OF EXAM	TESTS
Mental Status	Level of alertness and orientation. Assess attention using months forward/backward. Immediate registration and delayed recall of 3 objects for 4 minutes (timed). Naming of watch parts. Note behavior, language, affect, etc., while taking history.
Cranial Nerves	Pupil light reflexes. Ophthalmoscopic exam. Visual fields, including extinction testing. Horizontal and vertical smooth pursuit eye movements. Facial sensations to light touch including extinction testing. Facial symmetry during emotional smile. Hearing of finger rub bilaterally. Palate elevation. Note quality of voice during remainder of exam. Head turning and shoulder shrug against resistance. Tongue protrusion.
Motor Exam	Drift. Rapid hand and foot tapping. Upper and lower extremity tone. Strength in several proximal and distal muscles in the upper and lower extremities bilaterally (finger extensors, finger abductors, wrist extensors, biceps, triceps, deltoids, iliopsoas, quadriceps, foot and toe dorsiflexors, and knee flexors).
Reflexes	Bilateral biceps, brachioradialis, patellar, Achilles tendon, and plantar reflexes.
Coordination and Gait	Finger-nose-finger and heel-shin tests bilaterally. Gait and tandem gait.
Sensory Exam	Light tough in hands and feet, including extinction testing. Pin prick or temperature testing in feet bilaterally. Vibration and joint position sense in feet bilaterally

APPENDIX H. STATEMENT OF ORIGINAL WORK
ACADEMIC HONETY POLICY

Capella University's Academic Honesty Policy (3.01.01) holds learners accountable for the integrity of work they submit, which includes but is not limited to discussion postings, assignments, comprehensive exams, and the dissertation or capstone project.

Established in the Policy are the expectations for original work, rationale for the policy, definition of terms that pertain to academic honesty and original work, and disciplinary consequences of academic dishonesty. Also stated in the Policy is the expectation that learners will follow APA rules for citing another person's ideas or works.

The following standards for original work and definition of *plagiarism* are discussed in the Policy:

> Learners are expected to be the sole authors of their work and to acknowledge the authorship of others' work through proper citation and reference. Use of another person's ideas, including another learner's, without proper reference or citation constitutes plagiarism and academic dishonesty and is prohibited conduct. (p. 1)
>
> Plagiarism is one example of academic dishonesty. Plagiarism is presenting someone else's ideas or work as your own. Plagiarism also includes copying verbatim or rephrasing ideas without properly acknowledging the source by author, date, and publication medium. (p. 2)

Capella University's Research Misconduct Policy (3.03.06) holds learners accountable for research integrity. What constitutes research misconduct is discussed in the Policy:

> Research misconduct includes but is not limited to falsification, fabrication, plagiarism, misappropriation, or other practices that seriously deviate from those that are commonly accepted within the academic community for proposing, conducting, or reviewing research, or in reporting research results. (p. 1)

Learners failing to abide by these policies are subject to consequences, including but not limited to dismissal or revocation of the degree.

I have read, understood, and abided by Capella University's Academic Honesty Policy (3.01.01) and Research Misconduct Policy (3.03.06), including Policy Statements, Rationale, and Definitions.

I attest that this dissertation or capstone project is my own work. Where I have used the ideas or words of others, I have paraphrased, summarized, or used direct quotes following the guidelines set forth in the APA *Publication Manual*.

Learner name and date  Danielle Forshee, 6/17/14

Mentor name and school Dr. Mark Zwingelberg, Capella University