Exploration of Neurotransmitter Levels and Attention-Deficit/Hyperactive Disorder

by

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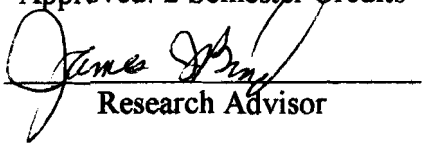
A Research Paper
Submitted in Partial Fulfillment of the
Requirements for the
Master of Science Degree
in

Guidance and Counseling

Approved: 2 Semester Credits



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December, 2006

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Title: ***Exploration of Neurotransmitter Levels and Attention-Deficit/Hyperactive Disorder***

Graduate Degree/ Major: MS Guidance and Counseling

Research Advisor: **James Byrd, Ph.D.**

Month/Year: **December, 2006**

Number of Pages: **52**

Style Manual Used: **American Psychological Association, 5th edition**

ABSTRACT

As the education of children continues to strive for improved success, school personnel find themselves wondering why children have developed into who they are. The notorious argument of nature verses nurture is at the root of our wonderment. This is particularly true when addressing the various needs of students, especially those diagnosed with one or more disabilities. One of the more popular disabilities is Attention Deficit/Hyperactive Disorder (ADHD), which is now defined by the Individuals with Disabilities Education Act (IDEA) as a qualifying disability to possibly be educated under an Individualized Education Plan (IEP). This is an indication of the impact ADHD can have on a student's ability to succeed in school. However, questions still remain as to what causes ADHD and what can be done for it. Yet, in order to answer those questions we must know what ADHD looks like, not only externally, but also internally. What is the Central Nervous System's (CNS's) role in this disorder? One way to look at it is by

examining neural cells, or cells in the CNS. More specifically, how do these cells communicate to impact attention and hyperactivity? It is known that neural cells communicate through chemicals called neurotransmitters.

The primary function of this study is to obtain and assess a specific neurotransmitter profile of children identified with ADHD. Specifically, the children construct a sample of ninety-seven special needs adopted children from southwestern United States. The neurochemical profile consists of the following eight neurotransmitters: Serotonin, dopamine, epinephrine, norepinephrine, phenylethylamine (PEA), gamma-aminobutyric acid (GABA), histamine, and glutamate.

In order to conduct this study, data collected by developmental researchers at Texas Christian University (TCU) was obtained and analyzed. It was hypothesized that a difference would be found between the neurotransmitter levels of children ages three to seventeen years old identified with ADHD and non-identified children of the same age group. Of the eight neurotransmitters measured, significantly higher levels of epinephrine were found.

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Acknowledgments

I would like to thank, first and foremost, the generous professors at Texas Christian University. Dr. Karyn Purvis and Dr. David Cross not only gifted the necessary data to conduct this project but also offered their extremely valuable time. For that I am forever thankful. Without them and the generosity of their assistants and NeuroScience, Inc. I could not have delved deeper into a sincere passion of mine – the health and well being of children. The same goes to my advisor, Dr. James Byrd, and the professors who guided me through this experience.

As I come to a close on this chapter of my life, I glance back and see the support of my friends and family. Without them this would be less meaningful. *Thank you God.*

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Chapter I: Introduction

The clinical diagnosis of Attention-Deficit/Hyperactivity Disorder (ADHD) has been referred to by the media as an epidemic. "According to the National Institutes of Health, more than a million children take prescription medication to control hyperactive behavior. The estimated cost to schools is about 3 billion dollars" (Chudler, 2005a, n.p.). Although the rate of diagnosis in school-age children, which is estimated at 3% to 7% (APA, 2000), is not technically an epidemic, the numbers are astronomical and there is widespread concern with what causes this disorder, how children are assessed/diagnosed, and what treatments are available.

ADHD is defined by the *Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition-Text Revision* (*DSM-IV-TR*) (APA, 2000) as "a persistent pattern of inattention and/or hyperactivity-impulsivity that is more frequently displayed and more severe than is typically observed in individuals at a comparable level of development" (p. 85).

As professional counselors we typically work with clients through relationship building and communication techniques. We see them prior to, during, after, or in place of various treatments with other professionals in the 'helping' field. Therefore, we carry the responsibility of having a knowledgeable background in all of those fields. This is due to the fact that at times we make referrals and collaborate with existing forms of treatment. New developments surrounding disorders such as ADHD are important because we need to be proactive in all aspects of our work.

School guidance counselors will likely be presented with concerns surrounding ADHD by parents, teachers, and students. Therefore, the purpose of this research is to increase comprehension of various features of the disorder. In particular, this paper will expand on the idea that imbalances in brain chemicals, called neurotransmitters, may be a key differentiator in a sample population of children not identified with ADHD and those identified. The sample consists of special needs adopted children from a metropolitan area in southwestern United States whose ages ranged from three to seventeen years old.

> There are no laboratory tests, neurological assessments, or attentional assessments that have been established as diagnostic in the clinical assessment of Attention-Deficit/Hyperactivity Disorder. Tests that require effortful mental processing have been noted to be abnormal in groups of individuals with Attention-Deficit/Hyperactivity Disorder compared with peers, but these tests are not of demonstrated utility when one is trying to determine whether a particular individual has the disorder. It is not yet known what fundamental cognitive deficits are responsible for such group differences. (American Psychiatric Association, 2000, p. 88-89)

The *DSM-IV-TR* does not recognize a test that quantitatively diagnoses ADHD. However, this paper will discuss a novel approach to assessing neurotransmitter levels that cannot diagnose ADHD, but may serve as a tool health care professionals can use to potentially screen for the presence of this disorder.

The neurochemicals considered in this study will consist of the following eight neurotransmitters: serotonin, dopamine, epinephrine, norepinephrine, histamine, glutamate, phenylethylamine (PEA), and gamma-aminobutyric acid (GABA).

Neurotransmitters are components of the nervous system that play an active role in day-to-day functioning of human beings. They are chemicals in our body responsible for communicating information in our brain to all other body parts (Neurotransmitter, 2003). The communication or movement of neurotransmitters is done between the cells of the nervous system, also known as neurons.

For various reasons miscommunication within the nervous system occurs and neurotransmitters become imbalanced. Dr. Eric Chudler (2005b) described four mechanisms that interrupt neurotransmitters. They are diffusion ("lost in space"), enzymatic degradation (deactivation), reuptake, and glial cells. Improper functioning of these mechanisms can cause an imbalance of neurotransmitter levels and ultimately affect how a person acts and feels.

One example of this is that an imbalance of histamine is responsible for the existence of allergies (and as stated further on, histamine is responsible for more than just allergies). As a result, allergy medications (antihistamines) attempt to compensate for the imbalance (Reich, 2001, personal communication).

Many drugs, legal and illegal, are used to alter the balance of neurotransmitters. Alcohol and methamphetamine are serious examples. In fact, psychotropic medications used to treat ADHD alter neurotransmitter balance as well.

In a world of drugs used to make people feel and act differently through neurotransmitter manipulation, we have yet to utilize neurotransmitter profiling as a tool for clinical diagnosis. Instead, we examine and observe how a client feels and behaves. In regards to ADHD, the tools used in diagnosis are primarily subjective in nature. However, long before neurotransmitter testing could be used as an objective assessment

tool, a correlation between neurotransmitters and the disorder would have to be greater understood. This study will explore the role of neurotransmitters in ADHD, as well as determine whether or not a correlation exists between urinary neurotransmitter testing and ADHD.

We will take a closer look at neurotransmitter levels in relation to ADHD by comparing the levels in adopted children ages three to seventeen identified with ADHD to non-identified children of the same age range. The ultimate goal is to better assist those affected by ADHD (doctors, parents, educators, and patients). In order to do so, a comprehensive literature review was conducted consisting of current beliefs as to what ADHD is, possible causes, prevalence, diagnosis, and treatments utilized. The review also contains the structure and definition of both inhibitory and excitatory neurotransmitters used in the profiles and how research indicates they relate to ADHD.

In the present study, the researcher collaborated with Texas Christian University (TCU). The Principal Investigators, Dr. Karyn Purvis and Dr. David Cross, along with their assistants, collected neurochemical data on the two said groups of children. A comparative analysis of the results was then conducted. It was hypothesized that a statistically significant difference of neurotransmitter levels between the two said groups exists.

Statement of the Problem and Purpose of the Study

The purpose of this study is to compare the neurotransmitter levels of serotonin, dopamine, epinephrine, norepinephrine, histamine, glutamate, phenylethylamine (PEA), and gamma-aminobutyric acid (GABA) in adopted children ages three to seventeen identified with an ADHD diagnosis and non-identified children of the same age range.

Texas Christian University (TCU), along with the children's guardians, conducted data collection procedures and NeuroScience, Inc. completed assays on the urinalysis kits in 2004.

Assumptions of the Study

It is assumed that parents and physicians identifying and diagnosing the children in this study were doing so correctly. It is also assumed data collection and analysis was accurately completed.

Definition of Terms

There are many terms that need to be defined for clarity and understanding. These are as follows:

Catecholamine – is "any of a group of amines derived from catechol that have important physiological effects as neurotransmitters and hormones and include epinephrine, norepinephrine, and dopamine" (Catecholamine, 2004, n.p.).

Dopamine – is a chemical naturally produced in the body. In the brain, dopamine functions as a neurotransmitter, activating dopamine receptors. Dopamine is also a neurohormone released by the hypothalamus…Dopamine is commonly associated with the 'pleasure system' of the brain, providing feelings of enjoyment and reinforcement to motivate us to do, or continue doing, certain activities. (Dopamine, 2005, n.p.)

Epinephrine – Also called adrenaline, epinephrine acts as a neurotransmitter within the brain and is also:

A hormone secreted by the adrenal medulla that is released into the bloodstream in response to physical or mental stress, as from fear or injury. It initiates many bodily responses, including the stimulation of heart action and an increase in blood pressure, metabolic rate, and blood glucose concentration. (Epinephrine, 2004, n.p.)

Gamma-aminobutyric acid (GABA) – is the primary inhibitory neurotransmitter in the brain, which is responsible for regulating the output of excitatory neurotransmitters, including glutamate. It "occurs in the central nervous system and is associated with the transmission of nerve impulses" (Gamma-Aminobutyric Acid, 2004, n.p.). According to the NeuroScience, Inc. *Technical Guide* (2003c), GABA acts as a "minor tranquilizer" and is affected by barbiturates and alcohol.

Glutamate –is "a salt or ester of glutamic acid, especially one that functions as a neurotransmitter that excites cells of the central nervous system" (Glutamate, 2004, n.p.). It acts as the primary excitatory neurotransmitter in the brain.

Histamine – is considered an excitatory neurotransmitter in the brain, as well as "a physiologically active depressor amine found in plant and animal tissue, derived from histidine by decarboxylation and released from cells in the immune system as part of an allergic reaction" (Histamine, 2002, n.p.).

Monoamine – is a neurotransmitter that contains one amine group and includes

norepinephrine, epinephrine, dopamine, serotonin, histamine, and phenylethylamine (PEA) (Monoamine, 2006).

Neurochemical Makeup – consists of the following neurotransmitters: serotonin, dopamine, epinephrine, norepinephrine, phenylethylamine (PEA), gamma-aminobutyric acid (GABA), histamine, and glutamate.

Neurotransmitters – are chemicals that are used to relay, amplify and modulate electrical signals between two neurons: the presynaptic neuron and the postsynaptic neuron (Neurotransmitter, 2005). A chemical can be classified as a neurotransmitter if it respects the following conditions:

1. It is synthesized endogenously; that is, within the presynaptic neuron
2. It is available in sufficient quantity in the presynaptic neuron to exert an effect on the postsynaptic neuron
3. Externally administered, it must mimic the endogenously released substance
4. A biochemical mechanism for inactivation must be present

(n.p.)

Norepinephrine – known as noradrenaline outside the USA…is also a neurotransmitter in the nervous system where it is released from noradrenergic neurons during synaptic transmission. It is one of the 'stress hormones' and affects parts of the human brain where attention and impulsivity are controlled. Along with epinephrine this compound affects the fight-or-flight response,

activating the sympathetic nervous system to directly increase heart rate, release energy from fat, and increase muscle readiness. (Norepinephrine, 2005, n.p.)

Normal children – For the purpose of this study, normal children are those who have not endured trauma beyond average development. This group of children displays behaviors and emotions deemed typical for their age group and do not have any diagnosed disorders.

Phenylethylamine (PEA) – an excitatory neurotransmitter that plays a role in cognitive function, PEA "has pharmacological properties similar to those of amphetamine, occurs naturally as a neurotransmitter in the brain, and is present in chocolate and oil of bitter almonds" (Phenylethylamine, 2004, n.p.).

Serotonin – has been shown to be in many representatives of the animal kingdom, in wasp stings and scorpion venom, in various fruits, such as pineapples, bananas, and plums, and in various nuts. It has been estimated that an adult human contains about 5 to 10 mg of serotonin, 90% of which is in the intestine and the rest in blood platelets and the brain. One role of the compound is as a neurotransmitter whose participation is being sought in diverse functions including learning, sleep, and control of mood. The structural similarity of serotonin to several drugs known to cause mental aberrations, such as LSD, has prompted much speculation as to the role of serotonin in naturally occurring mental disorders such as schizophrenia or depression. (Serotonin, 2003, n.p.)

Limitations of the Study

Limitations in this study are that some subjects may have been misdiagnosed. Such instances could affect the results of the study. Also, many of the children identified with ADHD were also identified with co-morbid disorders. Third, the participants did not discontinue use of any medications, which may have affected the data results. And finally, there was not a proper control group of non-adopted children without any psychological or neurological disorders and healthy, normal pre- and postnatal care.

Methodology

The methodology of this study consists of assessing a specific neurotransmitter profile of children identified with ADHD. The original data was collected by developmental researchers at Texas Christian University (TCU) in 2004 and was analysed by NeuroScience, Inc. The sample population of children is of ninety-seven special needs adopted children from southwestern United States. The neurochemical profile consists of the following eight neurotransmitters: Serotonin, dopamine, epinephrine, norepinephrine, phenylethylamine (PEA), gamma-aminobutyric acid (GABA), histamine, and glutamate.

Chapter II: Literature Review

In order to best understand the possible outcomes of this study, it is important to obtain a working knowledge of attention-deficit/hyperactivity disorder (ADHD), neurotransmitters, and how they relate to one another. The purpose of the literature reviewed is to gain such knowledge.

Attention-Deficit/Hyperactivity Disorder (ADHD)

What is ADHD?

Previously known as minimal brain dysfunction (Lauder, 1995; Denckla, 2003) ADHD is a disorder marked by dysfunction in "executive and attention-related abilities (poor concentration), increased motor activity (restlessness), and cognitive and [behavioral] impulsivity (ill-considered responses). Frequently associated are features of low self-esteem, emotional outbreaks and difficulties with delayed gratification" (Faraone and Doyle as cited in Oades et al., 2005, p. 122). ADHD is also likely to bring about aggression, hostility, and defiance (Lauder, 1995).

ADHD can have devastating effects on academics, marriages, careers, and may also increase vehicle accidents (King, Tenney, Rossi, Colamussi, & Burdick, 2003). The lack of impulse control is most detrimental to the judicial and social systems. However, most would agree it is significantly detrimental to the educational system and the patients themselves. Those who suffer from the disorder, first named in 1902 by the British physician George Still (Panksepp, 1998), are 32-40% more likely to drop out of school, 5-10% less likely to complete college, and 50-70% less likely to develop friendships than their normal peers (Barkley et al., 2002).

Causes.

"Although the exact aetiology of ADHD has not been determined, the related factors include familial and hereditary factors, prenatal or perinatal factors, chemotoxic factors, sociopsychological stress, structural and functional abnormalities of the brain, and developmental neurobiological factors in the regions of the brain related to ADHD" (Jensen, Mrazek, & Knapp, 1997 as cited in Cheon et al., 2003, p. 306). Confirming this is "the theory of Sagvolden and colleagues (2004) predicts that ADHD [behavior] results from the interplay between individual predisposition and the environment" (as cited in Oades et al., 2005, p. 128). Here we will briefly examine what the literature has said to support the two notions.

"The genetic contribution to [ADHD] traits is routinely found to be among the highest for any psychiatric disorder (70-95% of trait variation in the population), nearly approaching the genetic contribution to human height. One gene has recently been reliably demonstrated to be associated with this disorder and the search for more is underway by more than 12 different scientific teams worldwide at this time" (Barkley et al., 2002, p. 96-97). This is potentially large news since as of 1991, Goodman and Pollion (as cited by Ballard et al., 1997) completed research indicating although 48% of the literature reviewed at the time mentioned genetics as a cause for ADHD no gene had been located. There were only links to first- or second-degree relatives. Some argue "genetic tendencies are expressed in interaction with the environment" (p. 97) which include abnormal relationships, poor parenting skills, and stressful events.

In reviewing the book "ADHD: The Facts", written by Selikowitz, Szaniecki (2005) discovered "ADHD is primarily a genetic disorder where neurotransmitters are

affected and affects a whole series of brain functioning, which in turn gives rise to the symptoms" (abstract). Cheon et al. (2003) made mention of a dopamine transporter gene in reference to ADHD and genetics. Dr Eric Chudler (2005a) also stated the following:

> It appears that certain receptors in the brain which normally respond to the neurotransmitter called dopamine are not working properly. Most likely, dopamine is not being produced at normal levels in the brain. Recent work in adults points to a defect in an enzyme called dopa decarboxylase which helps make dopamine. This defect in dopamine production occurs in the anterior frontal cortex, an area associated with cognitive processes such as focusing and attention. (n.p.)

Neurotransmitters and ADHD are examined in greater detail in a latter section.

Along with a neurophysiological approach, which examines the chemicals of the brain, the structure of the brain is studied (Ballard et al., 1997). Head injuries are often cited as a probable cause to ADHD. This is most likely due to evidence that supports brain structural (lobe) dysfunction in relation to ADHD symptoms (Pliszka, McCracken, & Maas, 1996). The areas discovered through brain imaging studies that relate to the disorder are as follows: prefrontal cortex (Corman, Fedutes, & Culley, 2004), frontal area (Panksepp, 1998), basal ganglia (Lou, Hendriksen, Bruhn, Borner, & Nielsen; Heilman, Voeller, & Nadeau as cited by Rogeness, Javors, & Pliszka, 1992), and cortical/subcortical areas (Garber, Barber, & Spizman, 1990 as cited in Ballard et al., 1997).

Despite supportive brain imaging studies, some believe ADHD is caused by environmental factors such as boring classrooms, high demands for competition, and

stressed caretakers (Breggin; McCubbin & Cohen; Diller as cited in Faraone, 2005). "Increasingly, standardized educational expectations along with a growing intolerance of childhood playfulness may, in fact, be leading to more and more children being labeled with ADHD" (Panksepp, 1998, p. 91).

Whatever the cause, great care of humans should be taken from the moment of (and better yet prior to) conception as:

> experimental evidence indicates that behavioral abnormalities such as attentional deficits, hyperactivity, impulsivity, and learning disabilities can arise from in utero exposure to drugs used as antihypertensives, antidepressants, or antipsychotics that alter the function (and often the expression) of monoamine receptors. (Lauder, 1995, p. 157)

This leads us on a search for brain chemical links to ADHD.

Prevalence.

According to the *Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition-Text Revision* (*DSM-IV-TR*) (American Psychiatric Association [APA], 2000), 3% to 7% of school- age children are diagnosed with ADHD. Of those diagnosed, roughly 80% are combined inattentive and hyperactive/impulsive, 10-15% are inattentive, and 5% are hyperactive/impulsive (Rappley, 2005). It is one of the most notable reasons for referrals in schools (Brown, 2002).

In 1997, "close to 40% of children referred to mental health clinics [showed] symptoms of ADHD" (Ballard et al., 1997, p.1). Dr. Eric Chudler (2005a) estimated "AD/HD affects between 1.5 and 3.5 million school-age children in the U.S., or an estimated 5% of all boys and 2% of all girls" (n.p.). He stated he is not sure why there is

a difference between the two sexes. (As a side note: NeuroScience, Inc. (2005) has released a bulletin in which Volume 19 discusses a potential hormonal link to the sex differences associated with ADHD) Ballard et al. (1997) adds to these astonishing numbers by noting at that time 600,000 youngsters in the United States were taking medications for ADHD.

Tools used in diagnosis.

Although medications used to treat ADHD target neurotransmitters (as will be examined in a later section), current practice in diagnosis does not examine a client's neurotransmitter levels. Tools used to diagnose the disorder are subjective assessments conducted by doctors and primary caregivers. School personnel, such as teachers, can play an active role in assisting healthcare professionals characterize the disorder. Using multiple assessments across multiple settings can help ensure correct diagnosis of ADHD and minimize each other's limitations (Brown, 2000).

The assessment tools currently used for diagnosing ADHD are "structured interviews, behavioral rating scales, and behavioral observations" (Gibney, McIntosh, Dean, & Dunham, 2002, p. 540). Despite attempts to diagnose ADHD through neurocongnitive functioning, such as measuring brain activity while subjects engage in various activities, no neurological assessments have been established as being credible in assisting with diagnosis (APA, 2000).

The *DSM-IV-TR* (APA, 2000) has built the foundation for diagnosing ADHD and therefore assessments are based on the same criteria across the board. The Children and Adults with Attention-Deficit/Hyperactivity Disorder (CHADD) program is one of many

resources for those interested in learning more on the subject of ADHD, including symptoms and diagnosis.

In order to fall under the umbrella of ADHD, it is assumed the children in this study have displayed symptoms for a longer period of time than six months across two of the following settings: home, school, work, or social (CHADD, n.d.). There are three primary categories of ADHD defined in the *DSM-IV-TR* (APA, 2000): ADHD, Combined Type; ADHD, Predominantly Inattentive Type; and ADHD, Predominantly Hyperactive-Impulsive Type. There are general criteria set forth in order to be diagnosed with one of the three types. Specifically:

ADHD-Inattentive Type

- Fail to give close attention to details or makes careless mistakes.
- Has difficulty sustaining attention.
- Does not appear to listen.
- Struggles to follow through on instructions.
- Has difficulty with organization.
- Avoids or dislikes tasks requiring sustained mental effort.
- Loses things.
- Is easily distracted.
- Is forgetful in daily activities.

ADHD-Hyperactive Type

- Fidgets with hands or feet or squirms in chair.
- Has difficulty remaining seated.
- Runs about or climbs excessively.

- Difficulty engaging in activities quietly.
- Acts as if driven by a motor.
- Talks excessively.
- Blurts out answers before questions have been completed.
- Difficulty waiting or taking turns.
- Interrupts or intrudes upon others.

ADHD -Combined Type

- Individual meets both sets of inattention and hyperactive/impulsive criteria.

(CHADD, n.d., n.p.)

Treatment.

Dr. Eric Chudler (2005a) made mention on the *Neuroscience for Kids* website that the National Institutes of Health estimates roughly 1 million children take prescription medication as a form of treating symptoms for ADHD. Stimulant medications have been used to successfully treat its symptoms for 65 years (Denckla, 2003). However, 10-30% do not respond to or tolerate stimulant medications (Banaschewski, Roessner, Dittmann, Santosh, & Rothenberger, 2004). The first and currently only non-stimulant medication used to treat ADHD is Atomoxitine (Strattera).

The more common forms of medication include Methylphenidate (Ritalin), Dextroamphetamine (Dexedrine), Pemoline (Cylert), and mixed salts of amphetamine (Adderall) (Chudler, 2005a; Ballard et al., 1997). Drug therapy is aimed to alter the following three symptoms of ADHD: attention span, impulsivity, and concentration

(Ballard et al., 1997). Psychostimulant medications have not been shown to improve cognitive functioning (Denckla, 2003).

The most positive outcomes occur when medications are combined with behavior modification. Other ways to manage ADHD include accommodations at home, in school and other social situations (Barkley et al., 2002). Michael Brown (2000) adds to the list: parent training and counseling, individual and group counseling, social skills training, and client education. Unfortunately there is no cure at this time.

Neurotransmitters

What is a neurotransmitter?

The following quote taken from the book *From the Workshop of Discoveries* (as cited in Chudler, 2005b) was Otto Loewi speaking about his discovery of the first neurotransmitter:

> In the night of Easter Saturday, 1921, I awoke, turned on the light, and jotted down a few notes on a tiny slip of paper. Then I fell asleep again. It occurred to me at six o'clock in the morning that during the night I had written down something most important, but I was unable to decipher the scrawl. That Sunday was the most desperate day in my whole scientific life. During the next night, however, I awoke again, at three o'clock, and I remembered what it was. This time I did not take any risk; I got up immediately, went to the laboratory, made the experiment on the frog's heart, described above, and at five o'clock the chemical transmission of nervous impulse was conclusively proved. (n.p.)

Otto Loewi's frog heart experiment he mentioned in the quote was conducted only 85 years ago, in 1921 (Chudler, 2005b). He placed the first heart, which was

connected to the vagus nerve, in a chamber of saline. This chamber was connected to another chamber containing a second heart, allowing the flow of fluid. He stimulated the first heart with electrical impulses to the vagus nerve. Loewi observed the first heart slowing down followed by the second doing the same. He theorized there was a chemical released from the vagus nerve that flowed into the second chamber. "Vagusstoff" is what he called the chemical now known as acetylcholine; a neurotransmitter.

In order to understand neurotransmitters one must understand neurons. "The nervous system is a huge ensemble consisting of two distinct classes of cells: nerve cells or neurons, and glial cells or glia" (Gutierrez & Ormsby, n.d., n.p.). The human brain contains, to its best estimation, 10^{11} neurons. The characteristics of neurons are alike.

There are four parts to neurons: dendrites, soma (or cell body), axon, and presynaptic terminals (Gutierrez & Ormsby, n.d.). The neurons are capable of communicating to one another with the release of chemicals (neurotransmitters) from the presynaptic terminals of one neuron to the dendrites (or less likely the soma or axon) of another. This contact point between the neurons is known as the synapse. The space where the neurotransmitter is released is the synaptic cleft. The neuron that released the neurotransmitter is the presynaptic cell. The postsynaptic cell is the one receiving the message.

Figure 1. illustrates the structure of a neuron, and includes the following key components: axon, presynaptic terminal, and synapse.

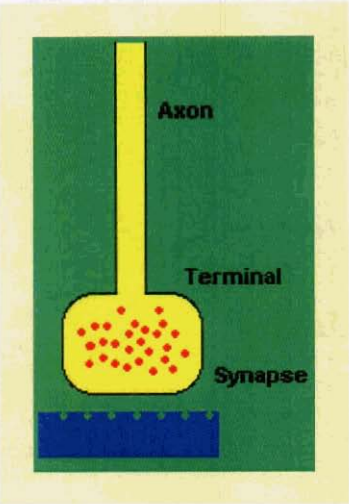

Figure 1. Neuron Structure. Image courtesy of *Neuroscience for Kids* (Chudler, 2005b, n.p.)

Just as there are guidelines to follow when diagnosing a client with ADHD, there are criteria to follow when classifying a chemical as a neurotransmitter. Figure 2 illustrates the criteria necessary for a chemical to be considered a true neurotransmitter.

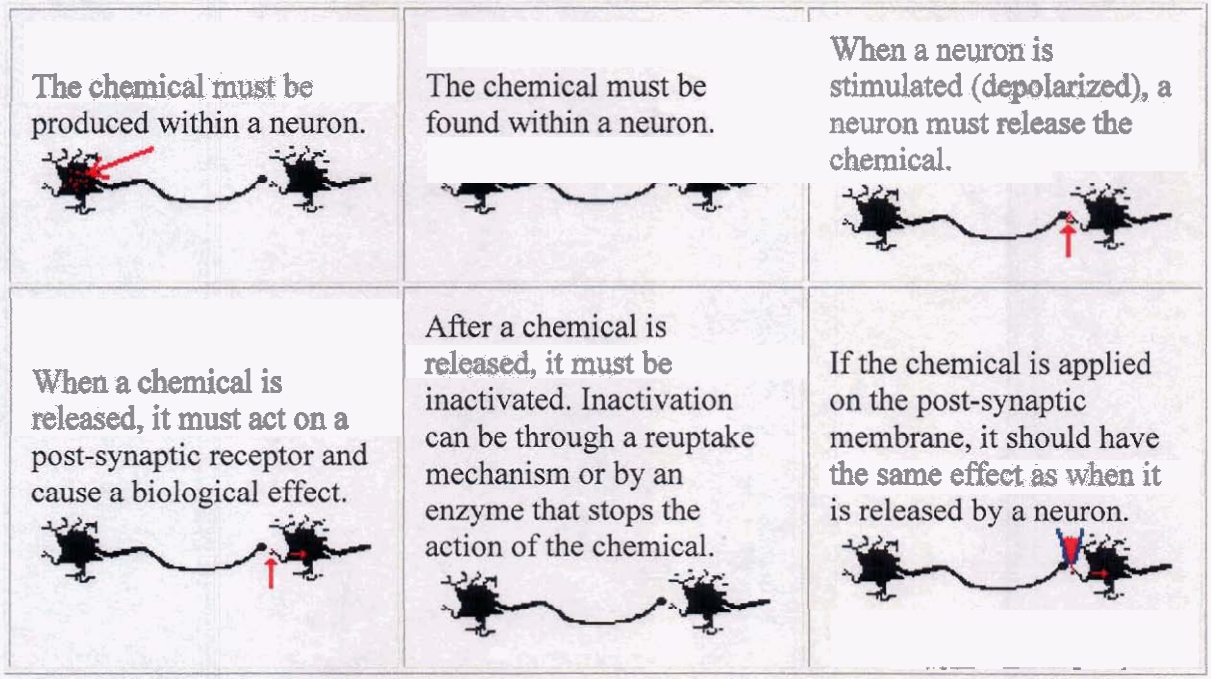

Figure 2. Neurotransmitter Criteria. Image courtesy of *Neuroscience for Kids* (Chudler, 2005b, n.p.,

The following are areas and means in which neurotransmitters are regulated: place of storage, receptor sites, precursors (such as tryptophan for serotonin), catabolic enzymes, synthetic enzymes, and other neurons (Rogeness et al., 1992). "One can look at the many steps in regulation as either many possible ways for a system to get out of balance or many ways in which a system may compensate if one part of the system gets out of balance.... The system may also be able to be in balance at normal activity but be unable to stay in balance during increased activity (when stressed)" (p.765)

Measurement of neurotransmitters.

> Basically all the monoamines can pass with varying degrees of ease passively or actively out of [central nervous system] tissue, although as acid metabolites do not equilibrate across the blood-brain membranes, they are sensitive to active transport mechanisms...However, measures derived from venous blood and urine often reflect challenges to the system, at least at a qualitative level. Peripheral and central monoamine activities are often correlated: if the correlations are not good, they are still strong enough to be relevant to the study of behavior. (Lambert, Horne, Kalff et al.; Pliska, Maas, Javors, Rogeness, & Baker as cited in Oades, 2005, p. 107).

How Attention Deficit/Hyperactivity Disorder (ADHD) and Neurotransmitters Connect

Inhibitory and excitatory neurotransmitters.

According to Coyle (as cited in Rogeness et al., 1992) the Central Nervous System (CNS) consists of at least thirty neurotransmitters which all have roles in various psychiatric disorders. The neurotransmitters are split up into two categories: inhibitory and excitatory. The excitatory transmitters increase the chances a signal will be relayed

between neurons while the inhibitory transmitters act to prohibit such signals (Neuroscience, 2003b). "For optimal functioning, the brain must balance the excitatory and inhibitory influences..." (n.p.).

The theory of imbalances is not uncommon. Rogeness and colleagues (1992) also believe a balance among the systems is a critical factor in the regulation of feelings and behaviors as the neuronal systems in the brain have been shown to interact with one another. In fact, a study conducted by Porges (as cited in Kalverboer, Genta, & Hopkins, 1999) supports the idea that hyperactivity is correlated with such imbalances: He "gave evidence for an imbalance between sympathetic (excitatory) and parasympathetic (inhibitory) systems in the brain in conditions such as hyperactivity..." (p. 165). Stahl (2003) went in a bit deeper by writing the following:

> Executive functions such as problem solving activate neurons in dorsolatoral prefrontal cortex and utilize numerous "smart" neurotransmitters, including dopamine, norepinephrine, histamine, acetylcholine, and perhaps others. Malfunction of the circuits that release these neurotransmitters can hypothetically lead to problems with executive functioning in numerous disorders, including attention-deficit /hyperactivity disorder...(abstract)

Groups of and individual neurotransmitters.

The following excerpts illustrate support found in the literatures that indicate each neurotransmitter's possible role in ADHD.

Dopamine, serotonin, and norepinephrine.

In examining studies, no pattern of difference in urinalysis of norepinephrine, dopamine, and serotonin has been found between subjects with ADHD in comparison to

controls (Rogeness et al., 1992). However, Rogeness and colleagues went on to write serotonin and norepinephrine in animals are important neurotransmitters in the role of assessing and attending to the environment and appears to be applicable to humans as well. The same two systems, along with the dopaminergic system, also regulate the internal restraint method (Depue and Spoont; Gray; as cited in Rogeness et al., 1992).

Cornings, Insel, Zohar, Benkefat et al., and Hanna, Yuwiller, and Coates (as cited in Lauder, 1995) found lower levels of serotonin, catecholamines, and their metabolites in those with ADHD. However, lower levels may not be the only signal of ADHD as Rogeness et al. (1992) demonstrate with a variety of hypothetical dopamine-serotonin-norepinephrine combinations and their likely outcomes. They believe the following likely result in ADHD and attentional problems: high dopamine with low norepinephrine and serotonin, low dopamine and norepinephrine with high serotonin, high dopamine and norepinephrine with low serotonin, low dopamine with low norepinephrine and serotonin, high dopamine with low norepinephrine and high serotonin, and high dopamine with high norepinephrine and serotonin. Getting back to the idea of balance among the systems as was discussed earlier may sum this up.

Dopamine (DA).

In the literature, dopamine (DA) may be the most commonly studied neurotransmitter in regard to ADHD. Animal studies, genetic studies, and imaging studies suggest dopamine plays an important role in regulating symptoms associated with ADHD (Konrad, Guaggel, & Schurek, 2003). It has been taken a step further by stating "attention deficit hyperactivity disorder (ADHD) is a psychiatric disorder in childhood that is known to be associated with dopamine dysregulation" (Cheon et al., 2003,

abstract). "At present the altered function of DA neurons is recognized as the main predisposing factor for ADHD" (Sagvolden, Pettersen, & Larsen as cited in Oades et al., 2005, p.128).

Dopamine decreases, rather than increases, response to new stimuli (Thierry et al. as cited in Pliszka et al., 1996). Experiments on rats have shown lesions on dopaminergic systems resulting in alterations in attention processing (Nieoullon, 2002). In children with ADHD the size of the prefrontal cortex and basal ganglia are 5-10% smaller than in normal children (Cheon et al., 2003). This supports the notion that dopamine transporters are decreased because these two areas consist of many dopamine receptors.

Eye blink rate studies, which are utilized to measure dopamine, indicate hypo-functioning of the dopaminergic system in children with ADHD (Konrad et al., 2003). However, "both hypo and hyper-dopaminergic states have been associated with increased hyperactivity" (Denckla, 2003, p.387). The question there remains as to how dopamine is an active player for both the attention deficit and hyperactive symptomology of ADHD.

Sagvolden, Petersen, and Larsen (as cited in Oades et al., 2005) theorized dopamine pathways are dysfunctional in those with ADHD in that they do not properly modify the inhibitory GABAergic or excitatory glutamatergic transmissions mediating behavior. "Thus, the integration of information about reinforcement associated with a particular event can be impaired by a dysfunctional mesolimbic DA pathway and exacerbated by a hypoactive glutamate input from frontal sources" (Grace as cited in Oades et al., 2005, p.125).

Gamma-aminobutyric acid (GABA).

"Gamma-Aminobutyric acid (GABA) is the major inhibitory amino acid in the brain" (Lauder, 1995). In other words, as pointed out earlier, GABA is the neurotransmitter that inhibits the likelihood a neurotransmitter will fire and send a signal. Dhossche et al. (2002) conducted a study on plasma GABA levels in nine children with ADHD and did not find differing levels in comparison to normal children. However, they cite another study (Prosser, Hughes, Sheikha et al.) in which plasma GABA levels in children with ADHD were higher than in their study. They conclude that further research is necessary.

Glutamate.

According to the NeuroScience, Inc. Technical Bulletin (2004a) high glutamate levels are commonly found in patients with ADHD. This is supported by a proton magnetic resonance spectroscopy study of the glutamatergic neurotransmitter system in children with ADHD. Moore et al. (2006) found "children with ADHD had a significantly higher ratio of glutamate plus glutamine to myoinositol-containing compounds than...healthy children" (abstract).

Serotonin (5-HT).

"Serotonin is an endogenous neurotransmitter that regulates aggressive and impulsive behavior and may be involved in the development of attention deficit hyperactivity disorder" (Li et al., 2005, abstract). Lesch and Merschdorf (2000) stated:

> genetically driven variation of 5HT system function, in conjunction with other predisposing genetic factors and with inadequate adaptive responses to environmental stressors, is also likely to contribute to impulsivity and aggression-

related behavior emerging from compromised brain development and from neuroadaptive processes. (p. 597)

Oades (2005) also adds "if one brings the separate findings together, there is an indication of an increase of 5-HT turnover, largely reflecting decreases in 5-HT levels" (p. 111). In other words, studies have shown for those with ADHD there is a high release rate of serotonin, which leads to lower levels of availability.

Phenylethylamine (PEA).

PEA is a major player in the field of ADHD. PEA was classified a neurotransmitter in 2001 (Neuroscience, 2003a). It increases alertness and activity in the brain leading to greater focus. Interestingly, PEA increases the efficiency of dopaminergic and noradrenergic neurotransmission (Paterson, Juorio, Berry, & Zhu as cited in Janssen, Leysen, Megens, & Awouters, 1999). Kusaga (2002) confirmed that by stating, "Beta-phenylethylamine (PEA), a biogenic trace amine, acts as a neuromodulator in the nigrostriatal dopaminergic pathway and stimulates the release of dopamine" (abstract). Janssen et al. (1999) report PEA and dopamine (along with amphetamine) are chemically related. Since dopamine is such an important neurotransmitter in the aspect of ADHD, it should be considered how PEA interacts with it.

There is some controversy regarding PEA levels in those with ADHD. Low levels have been associated in the literature (Baker et al. as cited in Janssen et al., 1999; Kusaga, 2002) where as Neuroscience (2003a) reports observing high PEA levels in those with symptoms seen in ADHD patients.

Histamine.

Arousal has been shown to correlate positively with the histaminergic system suggesting it also contributes to attentional, cognitive, and sensory processes (Schwartz, Arrang, & Garbarg, 2000). Neuroscience (2004b) reported finding higher levels of histamine in patients with ADHD. An interesting phenomenon is that histamine is marked with the presence of the GABA synthesizing enzyme glutamic acid decarboxylase; suggesting, yet again, there is relevance in the interaction of neurotransmitters in regards to clinical disorders such as ADHD.

Epinephrine (EPI or adrenaline) and norepinephrine (NE, noradrenaline, or NA).

Epinephrine (EPI or adrenaline) and norepinephrine (NE or noradrenaline or NA) play a part in activating the body's response to noise and stress, which requires the ability to switch attention from one stimulus to another (Pliszka et al., 1996). Studies show a positive correlation between EPI and cognition in normal children but not in those with ADHD, suggesting a role for EPI in ADHD (Konrad et al. 2003). "Analyses of CSF [cerebral spinal fluid], blood compartments, and urine indicate that in the ADHD condition MHPG levels (NE metabolite) are usually lower than normal: less clearly, NE levels may be increased. Overall this suggests a decreased turnover" (Oades, 2005, p. 111).

As supported by other studies (Hann, Ornitz, & Hariharan; Pliszka, Maas, Javors, Rogeness, & Baker; Anderson et al.; as cited in Konrad et al., 2003) "ADHD children seem to suffer from tonic overactivation of the NE system" (p. 431). Konrad and colleagues went on to write children with ADHD measured less epinephrine during "cognitive stress" than children in a control group and "the more ADHD symptoms the

lower the EPI excretion after cognitive stress" (p. 431). Finally, Pliska et al. (1996) supported this phenomenon as they wrote:

> Magnusson (1986) found that restlessness was negatively correlated with urinary EPI, while Klinteberg and Magnusson (1989) found urinary EPI to be lower in children with ADHD relative to controls. Pliska et al. (1994) also found urinary EPI to be lower in children with ADHD relative to controls. Tennes et al. (1986) found that NE/EPI ratio in normal children correlated positively with aggression and negatively with attentiveness. Thus, in contrast to higher NE activity than controls, children with ADHD may show lower levels of EPI activity. (p. 267)

Research suggests NE and the sympathetic nervous system impact attention and arousal (Konrad et al., 2003). More specifically, the locus ceruleus, which is primarily made of noradrenergic neurons, is supported by a large amount of data to play a role in attention processes (Berridge, Arnsten, & Foote as cited in Pliszka et al., 1996). It is also noteworthy that "levels of NE and DA in the extra cellular fluid are frequently correlated" (Janssen et al., 1999, p. 234) but that the noradrenergic system is important in responding appropriately to external stimuli and the dopaminergic system is important in responding to previously learned stimuli (Tassin as cited in Janssen et al., 1999). Again, the neurotransmitter systems interact with one another, reinforcing the belief they need balance in order to work in a healthy state.

Medication link.

"Various frequently used psychopharmacological agents (such as methylphenidate in ADHD) are thought to influence the functioning of [the inhibitory and excitatory] systems and eventually restore the balance between them" (Kalverboer et

al., 1999, p. 165). As previously mentioned 600,000 young Americans take medications for ADHD and the medications mimic neurotransmitters and their regulation (Ballard et al., 1997).

The following are areas and ways in which neurotransmitters are regulated in the body: their place of storage, receptor sites, precursors (such as tryptophan for serotonin), catabolic enzymes, synthetic enzymes, and other neurons (Rogeness et al., 1992). And, "there are pharmacological agents that alter function at each of these steps" (p. 765).

Most pharmacological drugs used to treat behavioral disorders interact with the neurotransmitters in the central nervous system (CNS) (Zimmerman, Jinnah, & Lockhart, 1998). "A useful framework for the evaluation and treatment of clinical behaviors incorporates current knowledge of the genotype and phenotype with knowledge of the neurotransmitters and their receptors affected in a given disorder" (p. 31).

The basic effects of most ADHD drugs manipulate dopamine and norepinephrine (Panksepp, 1998). "Dysfunctions of the catecholaminergic neurotransmitter systems are centrally involved in the pathophysiology of ADHD...and modulation of dopaminergic and noradrenergic neurotransmission in the prefrontal cortex by stimulants and noradrenaline uptake inhibitors appears to be a necessary mechanism for the effective treatment of ADHD" (Arnsten, Steere, & Hunt; Biederman & Spencer; & Spencer et al. as cited in Banaschewski et al., 2004, p. 1/102). Ballard et al. (1997) also stated the medications used to treat ADHD are designed to increase the release of catecholamines and mimic certain neurotransmitters. Although there is mounting evidence that supports drugs also affect serotonin (Lauder, 1995) and PEA, however the literature is slim. Here

we will take a look at the most common drugs prescribed in the treatment of ADHD and their effects on neurotransmission.

Stimulants: methylphenidate, amphetamine, dextroamphetamine.

In a study conducted by Zametkin et al. (1985) where urinary measures were taken from children with ADHD after ingesting methylphenidate, dopamine, PEA, and serotonin levels were not significantly changed but norepinephrine was. Within the same study PEA levels were increased 1,600% with dextroamphetamine. This is fairly contradictory, or perhaps too simply stated, in comparison to other literature reviewed.

First, NeuroScience, Inc. (2003a) reported a 20mg dose of methylphenidate increased PEA baseline levels five to ten times. Second, methylphenidate, along with other stimulant medications "primarily have dopaminergic and noradrenergic mechanisms of action, with blockade at the dopamine transporter reducing reuptake, resulting in an increase in the neurotransmitters at the synapse" (Swanson, 2003, abstract). This phenomenon of increased dopamine at the receptor site is supported by others as well (Cheon et al., 2003; Dopamine role in ADHD may explain drug's efficacy, 2001; Moll, Hause, Eckart, Rothenberger, & Huether, 2001; Oades, 2005; Oades et al., 2005). It is noteworthy that images showing areas in the brain that had increased blood flow with taking methylphenidate were areas with abundant dopamine receptors (Cheon et al., 2003).

Many studies have found medications such as methylphenidate, which increases dopamine, also increase epinephrine, suggesting the two closely interact (Konrad et al., 2003). Donnelly et al., Elia et al., and McCracken et al. (as cited in Pliszka et al., 1996) have shown through studies urinary epinephrine results increase due to stimulant

medication methylphenidate and dextroamphetamine. The fact that stimulant medications increase urinary epinephrine leads one to believe the reuptake of epinephrine is blocked or slowed (Pliszka et al., 1996).

In addition to strongly binding to the norepinephrine transporter, methylphenidate has a very weak interaction with the serotonin transporter (Oades, 2005) and also acts as a noradrenergic agonist (Quay, 1997).

Non-stimulants: atomoxetine.

"Increasing levels of NA, decreased postsynaptic neuronal firing and an enhanced tuning of response to signal versus noise result from modest doses of methylphenidate and atomoxetine" (Berridge and Waterhouse as cited in Oades et al., 2005, p. 127). Atomoxetine is "a highly selective inhibitor of the presynaptic noradrenaline transporter" (Banaschewski et al., 2004, p. 1/103). Stahl (2003) confirms atomoxetine is a selective norepinephrine reuptake inhibitor and therefore increases norepinephrine also along with dopamine. Of particular interest is that Atomoxetine may impact cognitive functioning in those with ADHD where stimulants have not been shown to.

Antidepressants: monoamine oxidase inhibitors (MAOI's), desipramine, bupropion.

Tricyclic antidepressants such as desipramine, nortriptyline, and imipramine have been successful in the treatment of ADHD (Banaschewski et al., 2004). "It is assumed that their activity in ADHD stems from their actions on catecholamine (noradrenaline and dopamine) reuptake" (p. 1/106). The antidepressant Bupropion, also used to treat ADHD, has effects on the dopaminergic, noradrenergic, and anticholinergic systems.

Antihypertensive: clonidine.

Clonidine is another medication shown to be effective in treating ADHD (Pliska et al., 1996). This is believed to be so due to a slower release of norepinephrine, which is supported by lower levels of plasma norepinephrine.

In summary:

> For many years, the fact that stimulant medications act as dopaminergic and noradrenergic agonists has lead to a 'catecholamine' hypothesis of ADHD. However, no comprehensive model had been explicated which successfully describes the underlying pathophysiology of ADHD and the mechanisms by which medications ameliorate its symptoms. (Pliszka et al., 1996, p. 264)

This is increasingly necessary as "evidence is slowly emerging that suggests that the long-term effects of drug exposure are delayed and expressed once the vulnerable system reaches maturation (i.e., typically during adulthood)" (Andersen & Navalta, 2004, abstract).

Chapter III: Methodology

The third chapter will focus on the methodology of this study. It will include a description of the sample population, how they were selected, the instruments used in this study and finally a look at data; how it was collected and the analysis procedures. The closing section of this chapter will include limitations to the methodology of this study.

Subject Selection and Description

In 2004, Texas Christian University (TCU) researchers Dr. Karyn Purvis and Dr. David Cross, along with their assistants, began researching the topic of behavior problems and neurotransmitter profiling in a sample of special needs adopted children. In order to conduct their study they recruited ninety-seven adopted children (ages three to seventeen) from fifty-seven families in southwestern United States. The families were recruited from support groups and all felt their children had varying special needs.

Upon agreeing to the TCU study, the parents were asked to fill out a history form on their child(ren). The history form included information regarding; risk factors such as prenatal and/or postnatal risk, abuse, neglect, and trauma; psychotropic medications such as anti-depressant, anti-psychotic, and allergy; and finally identified disorders.

Twenty-seven were identified with an attention-deficit/hyperactivity disorder (ADHD) diagnosis. Of the remaining fifty, twenty were identified with mood disorder, twelve with attachment disorder, and eleven with pervasive developmental disorder. Therefore, only seven were not identified with a diagnosed disorder.

This researcher has come into collaboration with TCU and the principal investigators have allowed the utilization of data from their original study in order to examine ADHD in closer detail. The researchers are currently publishing their data

regarding, as mentioned earlier, behavior problems along with neurotransmitter profiles. Dr. Purvis and Dr. Cross utilized the Child History questionnaire and Achenbach's Child Behavior Checklist along with the neurotransmitter profiles.

Instrumentation

According to Dr. G. H. Kellermann, owner of NeuroScience, Inc., urinary neurotransmitter levels were assayed in the laboratory using an Enzyme-Linked Immuno Sorbent Assay (ELISA). Sample preparation includes a series of centrifugations and dilutions with various buffers to arrive at a sample ready for the ELISA assay. The neurotransmitter ELISA assays are colorimetric, employing the use of a spectrophotometer for the final analysis of the respective transmitter levels in urine (personal communication, November 22, 2006).

Each sample was assayed for the following neurotransmitters: epinephrine, norepinephrine, dopamine, serotonin, gamma-aminobutyric acid, glutamate, phenylethylamine, and histamine, with quantities express in terms of parts per gram of creatinine.

Data Collection Procedures

For the purpose of this study, once subjects agreed to participate, TCU researchers supplied them with a NeuroScience, Inc. neurotransmitter urinalysis kit. The kits were comprised of a pre-stamped package, a collection cup, a pipette, a transport tube, and instructions for collecting the urine sample. The participants were asked not to eat for twelve hours prior to collecting the sample. They were to collect the second urine of the morning. Once the sample was collected in the cup, the urine was to be transferred to the tube with the pipette. The sample was to be frozen until shipped, via US Priority Mail to

the laboratory for analysis. Only the subjects' first name and identification number were submitted to NeuroScience, Inc. Upon receiving the sample at the laboratory, each was applied a separate, internal identification number. The samples were stored frozen until the laboratory was ready to begin assay preparation. The company donated the expenses of these procedures for the purpose of this study.

Data Analysis

Upon completion of the laboratory assays, the following data were provided for statistical analysis: a database containing neurotransmitter values for each of the ninety-seven participants, totaling seven hundred seventy-six data points was generated. Data were analyzed using a computerized statistics package called SYSTAT. The statistics ran consisted of two independent samples t-tests in order to determine whether significant differences exist between the individual neurotransmitters of the two groups of children. Urinary neurotransmitter testing is not considered diagnostic for any particular condition. As a Class I, 510 (K) exempt medical device, urinary neurotransmitter testing is not subject to FDA approval criteria. However, numerous studies, including many mentioned in this paper, have employed the use of urinary neurotransmitter testing as a valid means of assessing the various neurotransmitters.

Limitations

Unfortunately, there are several limitations to this study that will be identified here. First and foremost, this study lacks a proper control sample for comparative analysis. The analysis was done with the same sample population of adopted children who were identified by their parents as having varying degrees of special needs. And, all but seven of the fifty comparison children were identified with a disorder. Not only that,

but there was a high rate of co-morbidity in the sample of children identified with ADHD. The number of children identified only with an ADHD diagnosis was one.

Second, there is a lack of standardization in regards to how urinalysis results are reported, which would make them difficult to compare across studies. Third, the participants did not discontinue use of medications, which may have affected the data results. And finally, the sample size is relatively small and therefore generalization to the population should be done cautiously.

Chapter IV: Results and Discussion

In the final chapter, the results, which compared the neurotransmitter levels of serotonin, dopamine, epinephrine, norepinephrine, histamine, glutamate, phenylethylamine (PEA), and gamma-aminobutyric acid (GABA) in adopted children ages three to seventeen identified with an ADHD diagnosis and non-identified children in the same age range, will be concluded and discussed. A two independent samples t-test was performed. In previous chapters, an extensive literature review has been conducted. Finally, a discussion on the limitations, implications, and recommendations of those results will follow.

Item Analysis

A two independent samples t-test was used to compare neurotransmitter levels in ADHD children with non-ADHD children. For epinephrine, the mean for the ADHD children ($\bar{x}$ = 17.4) was significantly higher than that for the non-ADHD children ($\bar{x}$ = 12.4), $t(95) = 2.38$, $p = .02$.

The difference between ADHD children and non-ADHD children was not significant for the remaining neurotransmitters ($p<.10$). Figure 3 reports the means of each neurotransmitter tested for the ADHD children and the non-ADHD children.

Table 1. Mean Neurotransmitter Levels in ADHD and Non-ADHD Children

	ADHD	Non-ADHD
Epinephrine	17.4	12.4
Norepinephrine	78.5	63.8
Serotonin	137.8	134.8
Dopamine	190.3	171.9
Histamine	27.5	27.2
Glutamate	48.2	59.5
Phenylethylamine (PEA)	872.9	805.1
Gamma- aminobutyric acid (GABA)	8.5	7.8

Limitations

Unfortunately, there are several limitations to this study that will be identified here. First and foremost, this study lacks a proper control sample for comparative analysis. The analysis was done with the same sample population of adopted children who were identified by their parents as having varying degrees of special needs. And, all but seven of the fifty comparison children were identified with a disorder. Not only that, but there was a high rate of co-morbidity in the sample of children identified with ADHD. The number of children identified only with an ADHD diagnosis was one.

Second, there is a lack of standardization in regards to how urinalysis results are reported, which would make them difficult to compare across studies. Third, the participants did not discontinue use of medications, which may have affected the neurotransmitter levels.

And finally, the sample size is relatively small and therefore generalization to the population should be done cautiously.

Conclusions

This study is extensive in the realm of the literature on ADHD and neurotransmitters individually and in relation to one another. It is only the beginning of examing whether a relationship between ADHD and neurotransmitters exists.

The results are not conclusive enough to rely only on urinary neurotransmitter testing when assessing children with ADHD. The only inference that can be made is more research needs to be conducted while minimizing the previously described limitations and maximizing the closing recommendations. Although the results indicate so, there is no way to infer urinary epinephrine values alone are an indicator of ADHD. The results may only reinforce what the literature reports: epinephrine plays a role in attention processing. The same applies in that this study does not reinforce the literature review on the remaining seven neurotransmitters.

Recommendations

It is recommended that a proper control sample be used in comparing children with an ADHD diagnosis in order to determine whether a statistically significant difference exists in regard to their neurochemical profiles. It is also then recommended to control for co-morbidity and medications and profile children diagnosed only with ADHD and no other disorders. It is also suggested to utilize a behavior checklist, such as the Child Behavior Check List (CBCL) used in Dr. Purvis' and Dr. Cross' original study, in order to examine behaviors and neurotransmitters, since there are subtypes to ADHD (inattentive, hyperactive, and a combination of both).

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