ANN HEATHER CODY
Analysis of Developmental Variations in the Caudate Nucleus in Children with Attention-Deficit/Hyperactivity Disorder (ADHD)
(Under direction of GEORGE W. HYND)

Literature in the field of ADHD has implicated the role of neurological mechanisms in the behavioral symptoms seen in this disorder. Empirical research has been conducted in the areas of lesion studies, case analysis, neurotransmitters, and neuroimaging. Magnetic resonance imaging (MRI) one imaging technique that has been used to identify structural differences in neuroanatomy that can used in child populations. Most theoretical and empirical research to date has identified a dysfunction in the fronto-striatal pathway as being the neurological basis for ADHD. Specifically, the caudate nucleus is a subcortical structure that has been linked to the problems with motor regulation and behavioral inhibition seen in individuals with ADHD. This study used MRI to obtain area and volume measurements of the caudate nucleus in a group of children diagnosed with ADHD, aged 8-12 years of age. Comparisons of caudate size were made with a group of normal control children and a clinical group identified as reading disabled. Asymmetry patterns between right and left hemispheres were examined for group differences. Correlational analyses between measurements of the caudate nucleus and behavior ratings and neuropsychological test data were also conducted.

INDEX WORDS: Attention-deficit/hyperactivity disorder (ADHD), Behavior ratings, Caudate nucleus, Children, Executive functioning, Magnetic resonance imaging (MRI), Neuropsychology

ANALYSIS OF DEVELOPMENTAL VARIATIONS IN THE CAUDATE NUCLEUS IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)

by

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Date

DEDICATION

I would like to dedicate this dissertation to my parents, Jim and Tania Cody, who taught by example the values of hard-work, conscientiousness, persistence, and the importance of having a sense of humor. Their guidance and support helped me accomplish this project. I also wish to dedicate this dissertation to my younger sisters and brothers: Christana, Rachelle, Alyssa, Rebecca, James, Jennifer, Sharon, Caroline, and John. My interest in working with children grew largely out of my good fortune in having so many wonderful "teachers."

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TABLE OF CONTENTS

LIST OF TABLES

CHAPTER I

INTRODUCTION

In the clinical setting and in the schools, a number of children are referred for problems with inattention and/or hyperactivity. Approximately 3-5% of children are suspected of displaying symptoms of Attention-Deficit/Hyperactivity Disorder (ADHD), as reported by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV: American Psychiatric Association, 1994). This current edition of the DSM defines ADHD as a developmental syndrome involving inattention, impulsivity, and hyperactivity which significantly impairs a child's learning, social, and emotional functioning. The most recent revision of the DSM has created three distinct subtypes of the disorder, Primarily Inattentive, Primarily Hyperactive/Impulsive, and Combined Type. Yet the children who are diagnosed with this disorder have not always been delineated by these subtypes. Over the last few decades, the definition and label of ADHD has undergone a number of evolutions. However, the core behavioral features (hyperactivity, impulsivity, attention problems) have been examined and validated extensively in the literature (Goodyear & Hynd, 1992).

Based upon his factor analytic work, Hinshaw (1994) discussed two core behavioral dimensions that have been associated with ADHD. One cluster is comprised of symptoms of inattention, cognitive impulsivity, and occasional restlessness. The other cluster consists of problems of motoric overactivity and behavioral disinhibition. Investigation of the component of inattention by van der Meere, van Baal, & Sergeant

(1989) indicate that rather than evidence an inability to display sustained attention over time, ADHD children seem to have greater deficits in controlling motor output rather than in self-monitoring their attention. Specifically, these children are characterized by slowness in response output, which implicates the motor-intentional system as the underlying neurological mechanism involved, as opposed to attentional systems. Thus, the behavioral impulsivity typically seen in children with ADHD may be better explained by global disinhibition of behavior, which would characterize the symptoms of impulsivity in ADHD as dysregulated motor activity (Hinshaw, 1994).

The empirical research on ADHD remains somewhat divided between these hypothesized dysfunctions, and animal models for ADHD continue to be explored. The impetus to discover the true etiology of ADHD dominates much of the literature. Historically, ADHD was linked to dysfunction of the central nervous system, when physicians associated the behavioral symptoms of ADHD with those symptoms associated with brain injury. Behaviors resulting from head injuries and infections to the central nervous system were combined into a brain damage syndrome (Shaywitz & Shaywitz, 1989). Rutter (1989) stated that much of the reasoning used to characterize attention deficit disorders as the result of specific brain damage were circular in nature, for the behavioral symptoms themselves were viewed as being the proof of brain damage. In this framework, early classifications of hyperactive children were characterized as displaying "minimal brain damage" or "minimal brain dysfunction" (Strauss & Kephart, 1955).

One of the most problematic issues related to these early definitions was the variability in the types of symptoms that resulted in brain damage, which could include problems in attention and hyperactivity. Children with soft neurological signs and learning disabilities were also included in this classification. Eventually, children with hyperactivity and attention problems were distinguished from those with specific learning disability and other neurological syndromes, with hyperactivity being the primary diagnostic feature used for categorization of ADHD. When research failed to pinpoint the specific neurological structures involved in the brain damage associated with attention deficit disorders, the name evolved and the disorder became known as "hyperactive child syndrome" or "Hyperkinetic Reaction of Childhood" (Frick & Lahey, 1991). Shaywitz, Fletcher, & Shaywitz (1994) outlined the historical conceptualizations of ADHD graphically (see Figure 1).

There are several current theories about the etiology of ADHD, but to date no study has found a sole causative factor. In fact, it has been suggested that a number of etiological factors may result in the presentation of ADHD (Barkley, 1990). Genetic factors, prenatal and/or perinatal factors, food additives and refined sugar, allergies, and disturbances related to thyroid functioning have all been linked to the behavioral features of ADHD. While none of these theories have been proven conclusively, research leans most heavily toward a genetic predisposition (Biederman, Munir, Knee, Habelow, Armentano, Autor, Hoge, & Waternaux, 1986; Riccio, Hynd, & Cohen, 1997). Whitman (1991) reviewed the research in this area and found an increased prevalence of ADHD in the biological relatives of ADHD probands documented in a half dozen studies. Even

popular literature on ADHD has begun to espouse the notion that ADHD was the result of central nervous system dysfunction, as opposed to external factors such as sugar ingestion or brain injury (Wodrich, 1994). This may have reflected a growing acceptance by the public for neurobiological explanations of deviant behavior.

Weiss (1984) reviewed the various etiological factors implicated in ADHD and reached a relevant conclusion regarding this research. Children with ADHD have been found to display minor physical anomalies (e.g., ears, face) as well as learning disabilities which would suggest some congenital neurodevelopmental abnormality is associated with ADHD. As more research points to the role of genetics and variability in brain development in learning disabilities, such as dyslexia, the implications are that comorbidity between ADHD and learning disability reflect disturbances in brain development. Cantwell's (1984) review of the neurologic factors associated with ADHD concluded that children with ADHD who showed evidence for minor physical abnormalities also displayed greater degrees of hyperactivity, while those with soft neurological signs were typically better responders to pharmacological intervention. This observation supports the theoretical models implicating a neurodevelopmental dysfunction in these children.

Research examining pharmacological treatment also lends credence to a biological basis for ADHD. At one point, it was suggested that children with ADHD did not show evidence of structural brain damage, but rather a dysfunction in the metabolism of certain neurotransmitters (Weiss, 1984). Rutter (1989) described an important

characteristic of successful drug responders. Children with ADHD who appear to be the best candidates for stimulant treatment are those who seem to display pervasive (as

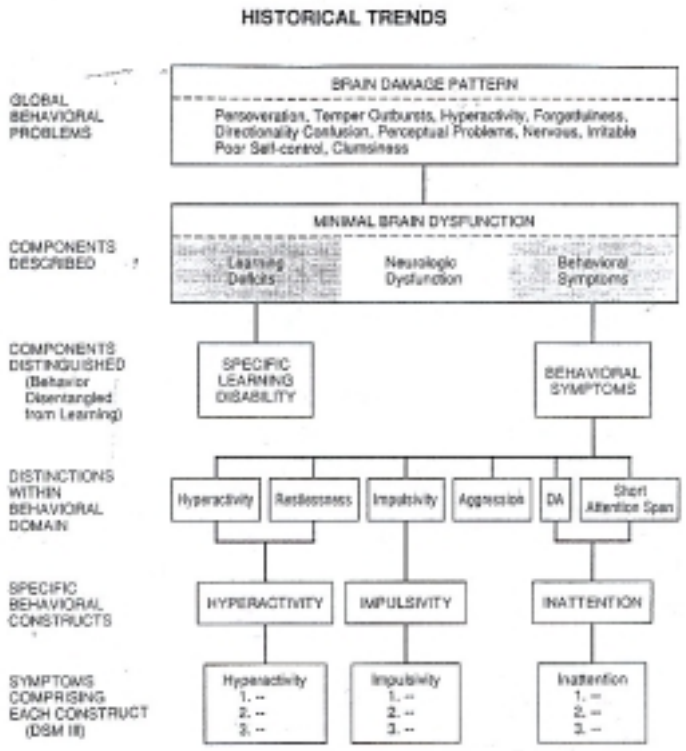

Figure 1. Historical conceptualizations of ADHD from Shaywitz, Fletcher, & Shaywitz (1994).

Figure 1. Historical conceptualizations of ADHD from Shaywitz, Fletcher, & Shaywitz (1994).

opposed to situational) features of the disorder. Pervasiveness reflects a severity level of the syndrome, it reasons that a child who displays more characteristics of hyperactivity and inattention across many different settings would appear to represent a more severe presentation of ADHD. Another important feature outlined by Rutter (1989) which suggests neurological involvement is the increased rate of neurodevelopmental immaturities (e.g., delays in language or motor development) in pervasive ADHD.

Perhaps the most persuasive empirical evidence to date has come from lesion studies and pharmacological experiments. Models for attention and hyperactivity have been validated through lesion analysis and controlled administration of stimulants. Specific theoretical models for a frontal-striatal dysfunction have emerged based upon findings that disruptions along this pathway can impair motor response initiation and inhibition. Greater focus has been placed on the influence of the striatum, which includes the caudate nucleus and putamen, on the behavioral presentation of ADHD.

The greatest advances in the search for a neurological basis of ADHD have been made during this last decade with the refinement of brain imaging techniques. Previously, research was primarily restricted to adults who could undergo more invasive procedures, such as cerebral blood flow (CBF) studies or positron emission tomography (PET) scans (e.g., Lou, Henriksen, Bruhn, 1984; Zametkin, Nordahl, Gross, King, Semple, Rumsey, Hamburger, & Cohen, 1990). However, the development of less invasive procedures to study the living brain, such as magnetic resonance imaging (MRI), opened new avenues for research with younger populations. As suggested by Rutter (1989),

> "...there is much value in the search for a possible specific biological basis to the syndrome (or, rather, possible bases as the condition may well prove to be heterogeneous). In that connection there is a need for systematic genetic studies, for the use of non-invasive brain imaging techniques that can study active brain function, and for computerized EEG studies studying brain functioning in relation to task performance... (p.18)."

Need for Further Research

In adults, damage to the caudate nucleus has been shown to result in a behavioral presentation akin to ADHD (Mendez, Adams, & Lewandowski, 1989; Petty, Bonner, Mouratoglou, & Silverman, 1996). Studies with children and adolescents have been less frequent, but some authors have found evidence for a smaller anterior cortex in children with ADHD (Hynd, Semrud-Clikeman, Lorys, Novey, & Eliopulos, 1990). Further work has also shown reduced volume of the corpus callosum may also exist in this population (Giedd, Castellanos, Casey, Kozurch, King, Hamburger, & Rapoport, 1994; Hynd, Semrud-Clikeman, Lorys, Novey, Eliopulos, & Lyytinen, 1991). Finally, other research has documented a smaller caudate nucleus in children with ADHD (Castellanos, Giedd, Eckburg, Marsh, Vaituzis, Kaysen, Hamburger, & Rapoport, 1994; Filipek, Semrud-Clikeman, Steingard, Renshaw, Kennedy, & Biederman, 1997; Hynd, Hern, Novey, Eliopulos, Marshall, Gonzalez, & Voeller, 1993; Mataro, Garcia-Sanchez, Junque, Estevez-Gonzalez, & Pujol, 1997). However, while these studies support the theoretical assumption of a dysfunction in the frontal-striatal pathway, there have been questions as to which hemisphere may be involved. Although evidence has begun to accumulate

showing that the head of the left caudate nucleus may be smaller in ADHD subjects than normal children, there are still discrepancies among studies. Additionally, few studies have compared the size of the caudate nucleus to behavioral symptomatology in children. It may be that severity of presentation is reflected in greater morphological differences in the caudate nucleus for children with ADHD.

In Chapter II, the literature supporting a neuroanatomical model for ADHD will be reviewed. First, theories involving the substrates of attention and impulsivity will be discussed as they relate to ADHD. In particular, the role of the basal ganglia (which is comprised of the caudate nucleus and putamen) in behavior will be examined in the context of ADHD. Next, the various types of research supporting the role of the caudate nucleus in inhibition will be reviewed. Research conducted in lesion studies (animal and human populations) and pharmacological work will be discussed and the available imaging studies reviewed in depth. The goal of this review will be to articulate the theoretical basis and experimental research that implicates the caudate nucleus in ADHD. Chapter II closes with a statement of the problem and a description of the goals of this investigation. Among these is the hope to find differences in caudate nucleus size between groups of children with ADHD, a clinical sample, and normal controls. Additionally, caudate nucleus size will be examined in relationship to selected behavioral variables. Chapter III describes the methodology used to explore these investigations. In Chapter IV, the results of the data analyses are reported. Finally, these results are discussed in Chapter V as they relate to previous research findings in the literature and

their implications for further research. A discussion of the limitations of this study is also included in Chapter V.

CHAPTER II

REVIEW OF THE LITERATURE

The neurological mechanisms which appear to be involved in ADHD can be conceptualized in a number of different ways. There are brain structures which play a role in attention and motor behavior, neurotransmitters that allow for the communication between neurons, and pathways which are influenced by other brain mechanisms. Most likely, the inattention and motor disinhibition of ADHD result from the interaction between all of these factors. In order to understand the current theories of neurological basis for ADHD, research involving lesion studies, neuropharmcological experiments, and brain imaging studies will be discussed. Each line of research sheds some light on what neurobiological mechanisms are involved in ADHD.

In their review of the research regarding the neurobiology of ADHD, Riccio, et al., (1997) discussed the possibility of two neural systems, each playing a distinct role in the processes comprising attention. The left hemisphere may be responsible for an activation system. This system would specialize in analytic and sequential cognitive operations. Dopamine would be involved in the modulation of this system. The right hemisphere would house an arousal system, responsible for holistic, parallel, and novel cognitive functions. This system would be modulated by norepinephrinergic neurotransmitters.

This conceptualization would explain the different results obtained by researchers who seek to localize the behavioral manifestations of ADHD. Further, both anterior brain

structures and posterior brain structures have been implicated in ADHD, and behavioral and neuropsychological evidence seems to differentiate children with and without hyperactivity (Goodyear & Hynd, 1992; Schaughency & Hynd, 1989). Children with hyperactivity and impulsivity seem to have more involvement in the anterior regions, such as the frontal lobes, while children who do not exhibit these behavioral features appear to show more activation in posterior regions, such as the parietal lobes (Chelune, Ferguson, Koon, & Dickey, 1986). Grodzinsky and Diamond (1992) also found evidence for dysfunction related to the frontal lobes in a group of adolescent males diagnosed with ADHD.

The model proposed by Voeller (1991), provides the best explanation for the various types of behaviors associated with ADHD. This model takes into account the role of neuroanatomical structures as well as the involvement of neurotransmitters. The model describes two distinct pathways, an ascending pathway responsible for arousal mechanisms, and a descending pathway responsible for inhibitory mechanisms. These pathways involve connections between the frontal lobes, basal ganglia, and the thalamus. Voeller (1991) hypothesized that neurotransmitters reach various cortical structures via the ascending pathway. When this pathway is disrupted, adequate levels of arousal may not be maintained in the endpoint, such as the frontal lobes. Conversely, the descending pathway provides an exit route for neurotransmitters to leave the cortical areas, allowing for the inhibition of certain behaviors. When this pathway is dysfunctional, inadequate inhibition is the result. There is some empirical evidence to support Voeller's hypothesis. Selemon & Goldman-Rakic, 1990 found that the parietal, frontal, and limbic pathways

terminate in the caudate, implicating the basal ganglia structures as a center of influence over the thalamus and motor structures. In his review of the neurochemical aspects of ADHD, Desch (1991) implicated a similar relationship between frontal and midbrain structures such as the thalamus, caudate, and hippocampus.

Further support for this model had been postulated by Posner and Petersen (1990). They hypothesized that there were actually three attentional networks based upon correlations to specific brain pathways. The orienting/shifting (selective) attention network is localized to the bilateral superior parietal lobes, thalamus, and midbrain. This network would be responsible for disengaging and reorienting attention to new stimuli. The executive network is localized to the anterior cingulate and basal ganglia (which contains the caudate nucleus). The executive network would be responsible for detecting objects and bringing them into conscious awareness. Finally, the alerting/arousal (vigilance) network is localized to the right frontal lobe (in the region of Brodmann's area 6) and would be responsible for maintaining an alert state.

Kaufman (1994) discussed the two models of animal research used to investigate the neurobiological basis of ADHD. The first methodology focuses on examining a particular behavioral symptom of ADHD (e.g., hyperactivity) and tries to reproduce it in animal studies, using their findings to establish the chemical and anatomic correlates. The second methodology works in the reverse by targeting a particular brain structure or pathway, disrupting the functioning of this mechanism, and correlates the behavioral outcomes with symptomatology found in children with ADHD. Research with animal subjects indicate that the head of the caudate nucleus contains circuits connecting

different regions of the frontal lobe with the thalamus and the cerebral cortex. Alexander, DeLong, and Strick (1986) described two pathways, based upon their research linking the basal ganglia to the cerebral cortex. The dorsolateral prefrontal and lateral orbitofrontal pathways each pass through the head of the caudate nucleus. Other research with monkeys has found that the cortical layers 2 through 6 in the prefrontal cortex send projections to the caudate nuclei (Arikuni & Kubota, 1986*;* Royce, 1982).

The work of Cummings (1993) outlines five frontal-striatal circuits, all originating in specific areas of the frontal lobes and traveling to the thalamus via the caudate nucleus. This would mean that lesions in the caudate would effectively disconnect the frontal cortex from subcortical and limbic structures. The first circuit described by Cummings is a motor circuit stemming from the supplementary motor area and traveling through the ventral caudate to the globus pallidus and terminating in the thalamus. The second circuit ("oculomotor") originates in the frontal eye fields and passes through the central body of the caudate. Of particular interest for the study of behavior is the third circuit, which passes from the dorsolateral prefrontal cortex through the dorsolateral head of the caudate. Lesions in this circuit result in difficulties with executive function and motor programming. Evidence for this third circuit has been documented in subjects with ADHD. Behavioral investigations examining children with ADHD indicate that the behavioral deficits exhibited by these children represent a dysfunction of the frontal-striatal axis (Heilman, Voeller, & Nadeau, 1991*;* Trommer, Hoeppner, Lorber, & Armstrong, 1988*).* Other work (Lou, Henriksen, Bruhn, Borner, & Nielsen, 1989) looking at the metabolic activity (with cerebral blood flow (CBF) studies) in subjects with

ADHD found decreased areas of metabolism in the basal ganglia, and especially in the right caudate nucleus. However, no behavioral test data was gathered in this study to associate the metabolic differences with diminished functioning. Barkley (1995) noted that problems with inhibition could underlie the hyperactivity and impulsivity in children with ADHD. These children would therefore have poorer impulse control due to a dysfunction in their inhibitory system. Barkley (1995) went on to hypothesize that this dysfunction may be caused by neurotransmitters that are not functioning properly to inhibit certain behaviors.

Returning to Cummings (1993) conceptualization, a fourth circuit originates in the lateral orbitofrontal cortex and projects through the ventromedial cortex. Lesions in this circuit can result in personality changes, disinhibition, inappropriate behaviors, irritability, imitation, and overstimulation by environmental cues. The fifth and final circuit described by Cummings travels from the anterior cingulate gyrus through the ventral portions of the caudate nucleus. Lesions in this circuit can result in akinetic mutism. It is the third circuit that bears most relevance to the other theoretical models proposed.

A similar model implicating a right hemispheric dysfunction as underlying the behavioral symptomatology of ADHD was presented by Schaughency and Hynd (1989). They hypothesized that deviations in normal cortical and subcortical development were related to the disturbances in anterior and posterior regulatory and attentional functioning, particularly in the right hemisphere. A dysfunction in the regulatory processes can be conceptualized as resulting in difficulties with inhibition and impulsivity. This model

proposed by Schaughency and Hynd (1989) is therefore similar to the frontal-striatal model described by Cummings (1993).

In a review of the neuropharmacology of the stimulant methylphenidate (Ritalin), Gaultieri and Hicks (1991) examined the existing pharmacologic research with children with ADHD. They concluded that the mitigating action of stimulants in children with ADHD was to reduce the variability in their levels of arousal and reactivity. They proposed a hypothesis that ADHD may be viewed as a dsyregulatory disorder localized to the frontal lobes, and in particular, the caudate nucleus. They based their hypothesis on biological information indicating that the frontal lobes receive and act upon almost all bilateral sensory information from sensory cortex and they are at the rostral end of a massive inhibitory and synchronizing system. The authors further supported their postulate by referencing clinical research comparing children with ADHD to patients with frontal lobe damage (e.g., both groups have distractibility, lack of impulse control, hyperactivity, attentional difficulties, and diminished self-regulation).

These theoretical models have been given more credence by other work that has examined the roles associated with specific brain structures or pathways. In relationship to the current study, the research emphasizing the functions of the basal ganglia and the caudate nucleus as they relate to ADHD will be discussed below.

Neurobehavioral Role of Basal Ganglia and Caudate Nucleus

The most persuasive studies linking neuroanatomical structures to ADHD implicate the role of the frontal lobes and associated subcortical structures which help monitor arousal and attention. The frontal lobes, a region of the cortex associated with

motor planning, problem solving, organizing, and executive functioning, have long been implicated in ADHD (Riccio, et al., 1997). While it is likely that the frontal lobes play an essential role in the behavioral presentation of ADHD, there is controversy in the literature due to mixed neuropsychological findings. Certain similarities between frontal lobe dysfunctions and "hyperkinetic" disorders have been found, which support the role of the frontal lobes in the symptoms associated with ADHD. Shared behaviors include attention and/or distractibility, perseveration, minor motor abnormalities, impulse control, frustration tolerance, planning and judgment, socially disapproved behaviors, and emotional lability (Conners & Wells, 1986).

The basal ganglia are a set of grey matter subcortical structures comprised of the caudate nucleus and the putamen. The caudate nucleus has been described as an inhibitory structure that integrates sensory information needed to inhibit behavior. Damage to the caudate typically results in involuntary movements, such as those seen in some movement disorders. For example, a dysfunctional caudate has been implicated in the intrusive, compulsive behaviors associated with obsessive compulsive disorder (Koziol, 1993). Damage to or dysfunction associated with the head of the caudate has been implicated in disturbance of higher order cognitive functions and in the movement disorders, such as Huntington's disease (Graybiel, Aosaki, Flaherty, & Kimura, 1994).

The caudate is connected by a thick bundle of fibers to the frontal lobes in a projection referred to as the caudate-frontal axis. Other terms have named this general pathway the "frontal-striatal system." This pathway has been associated with motor regulation and behavioral inhibition (Riccio, et al., 1997). This connection becomes

important when considering the behaviors associated with ADHD. Motor arousal and restlessness which originate in the striatal regions may be controlled in the frontal lobes (Cherkes-Julkowski, Sharp, & Stolzenberg, 1997). Given this conceptualization, the hyperactivity and impulsivity seen in these individuals with ADHD may reflect an inability to control the behavioral outputs of the basal ganglia. Borchgrevink (1989) proposed that ADHD is compatible with predominant frontal cortex pathology, specifically prefrontal and/or premotor. In his conceptualization, this pathology leads to impaired "top-down"

activation of voluntary behavior and poor integration of complex sequential functions including motor, speech, and memory span impairment.

Early research implicated the caudate-frontal axis to behaviors typical of ADHD, but were unable to back their theoretical models with empirical data. More recently, these behaviors (e.g., impulsiveness, disinhibition) have been related to an underlying dysfunction in dopamine circuits located between prefrontal and striatal centers. All of these hypotheses regarding the likely pathways involved in ADHD remain at the theoretical level until some of the behavioral characteristics (e.g., hyperactivity, inattention) can be localized to a particular brain location or systems. Once specific brain structures and systems are defined, better paradigms may be devised to learn more about the relationship between brain and behavior. One way to gather this type of information is to damage (lesion) an area and observe the behaviors that result from this damage. This can be done in animal research, and there are a number of animal studies already in existence that support neurological models for ADHD. However, this type of

research can not be done with human subjects. What can be accomplished, however, is the reporting of cases that involve some sort of lesion in a relevant brain area. Despite the limitations of case study investigations, lesion analysis is important in making direct associations between brain structures and behavior.

Lesion studies

Historically, lesion studies have found an association between the striatum and hyperactivity. Lesions in the striatum have been found to produce hyperactivity in both rats and monkeys (Kaufman, 1994). The work of Heilman and his colleagues (Heilman, Schwartz, & Watson, 1978; Heilman, Voeller, & Nadeau, 1991) has demonstrated that the behaviors seen in children with ADHD could be explained by a dysfunction of the right-sided striatum frontal axis. This disruption would impair motor response initiation and inhibition. For example, the fronto-striatal axis would be responsible for "filtering" motor responses. Other work by Heilman (Heilman & VanDen Abell, 1979) documented evidence for right hemisphere involvement in attention.

Orbital frontal lesions have been found to produce disinhibition, lack of drive, distractibility, impulsivity, and in some cases aggression (Stuss & Benson, 1984). In his review, Koziol (1993) conceptualized the deficits in sustained behavior, response inhibition, and hyperactivity associated with ADHD as resulting from functioning of the cortical-subcortical brain systems. The caudate has also been implicated in working memory functioning. Using a radial arm maze task, Packard and White (1990) found that lesions of the caudate nucleus in rats impaired the acquisition of reference memory but did not affect their working memory. Lesions of premotor cortex in macaque monkeys

produced monkeys who were unable to inhibit their responses in a structured paradigm and behaved in a repetitive and impulsive manner (Rizzolatti, Matelli & Pavesi, 1983*).*

Additional links between the motor impersistance (e.g., the inability to sustain a simple motor task) and the striatum have also been found. Voeller & Heilman (1988; 1989) found that motor impersistance improves after administration of methyphenidate, and cortical and striatal lesions in adults have been found to produce motor impersistance (Kertesz, Nicholson, Cancelliere, Kassa, & Black, 1985*).* As mentioned earlier, motor impersistance is the characteristic demonstrated by Voeller (1988, 1989) to be most related to the manifestation of ADHD.

Lesions in the midbrain regions of rats, specifically the ventral tegmental area (VTA) have been found to produce a syndrome which mimics ADHD. Behaviors which result from these lesions include locomotor hyperactivity, hyper-reactivity, poor frustration tolerance, disorganized behaviors, and hypomotivity (LeMoal, Stinus, & Galey, 1976). Furthermore, the intensity of these symptoms increased with the size of the lesion. In humans, lesions in the caudate have been associated with increased activity or "overactivity" (Caplan, et al., 1990).

Perhaps the most interesting study of a pathological disorder with direct relevance to the search for a neurological basis for ADHD is the work done with Huntington's disease. Huntington's is a progressive degenerative disease which primarily destroys the caudate nuclei and results in global dementia and motor impairments. However, in the early stages of Huntington's disease, patients may present as disinhibited, impulsive, apathetic, or display poor judgment. Neuropsychological testing with these patients

indicates specific difficulties with planning, organizing, sequencing, initiating activities, and poor immediate recall (Caine, Hunt, Wingartner, & Ebert, 1978; Folstein, Folstein, & McHugh, 1979). Through research in Huntington's disease, it is apparent that the role of the caudate nucleus is closely related to the prefrontal cortex. For example, there are numerous neural connections between the caudate and prefrontal cortex, through other structures such as the basal ganglia and thalamus.

Because of the ethical limitations of doing lesion studies on human subjects, much of the research in this area has focused on case studies and naturally occurring damage to the caudate nuclei. Richfield, Twyman, and Berent (1987) reported a case of a 25 year old female who suffered bilateral damage to the head of the caudate nuclei resulting from lesions of unknown etiology. The patient had no prior history of neurological or psychiatric disease and was seen after suffering from daily headaches and nausea for a period of several months. Background information revealed that she had been an honors student in high school, was employed and living independently, and was engaged to be married. The woman presented with uncharacteristic behaviors such as vulgarity, impulsiveness, easy frustration, violent outbursts, hypersomnia, enuresis, indifference, wandering, increased appetite, polydipsia, hypersexuality, inappropriate behaviors (e.g., shoplifting), and poor hygiene. One year following her examination, the woman was unemployed, divorced, and continued to exhibit these behaviors. The authors concluded that this case presented support for the hypothesis that the caudate neuclei are involved in processing information (e.g., organization, executive functions) in the prefrontal cortex as well as influencing the control of impulsive behaviors.

Similar findings were presented in a case study reported by Petty, Bonner, Mouratoglou, and Silverman (1996). The authors reported on the case of a 67 year old man who has infarctions in the head of the caudate bilaterally, the head of the thalamus bilaterally, had large cerebral ventricles, and periventricular lucencies. The patient was characterized as elated, jocular, disinhibited, and having loud and pressured speech that was difficult to interrupt. In addition, he was difficult to engage, had trouble maintaining his attention, and showed poor concentration and severely impaired short-term memory. While this case lends itself to speculation as to the role of the caudate in these behaviors, the fact that the neurological damage was not limited to the region of the caudate nucleus excludes the reader from reaching any specific conclusions.

Mendez, Adams, and Lewandowski (1989) studied 12 older adult patients who had lesions in the caudate nucleus (11 were unilateral, while one was bilateral). These lesions were documented through CT and MRI scans, and 7 patients were administered a neuropsychological battery of tests. This group found that the patients differed significantly from age-matched controls in three major ways. The patients were impaired on measures of problem-solving ability, had impairments in their immediate and delayed recall, and displayed significant limitations in their attention. All 12 patients were characterized into three groups, based upon their behavioral presentations. Group 1 were described as being apathetic with reduced spontaneity and initiative, Group 2 were disinhibited, inappropriate, disorganized, and unkemp, and Group 3 had affective disturbances (e.g., anxiety, depression). Of these groups, Group 2 is perhaps the most behaviorally similar to the presentation of ADHD. This group tended to have smaller

lesions which were primarily confined to the ventromedial area of the caudate. The researchers hypothesized from their work that the caudate nuclei may have a primary role in both behavioral and cognitive functions, in processing information related to prefrontal cortex, and in integrating information.

A comprehensive meta-analysis conducted by Bhatia and Marsden (1994) examined a total of 240 patients with lesions in the caudate nucleus, putamen, and globus pallidus reported through 1992. The lesions were primarily the result of vascular infarction or hemorrhage, but cases due to other traumas (e.g., tumor, angioma, hypoxia) were included. The authors excluded those patients suffering from degenerative diseases. The results were presented in terms of percentages. The cases were separated into groups according to the size of the lesion (small or large) based upon examination of CT and MRI scans. Out of all the cases, there were a total of 43 who were identified with isolated damage to the caudate nucleus (39 unilateral damage, 4 bilateral damage). Seventy-seven percent of the cases with small caudate nucleus lesions had behavioral and cognitive problems. In fact, lesions of the caudate nucleus were described as causing a behavioral problem (39%) more often than a motor disorder (20%). The authors reached two conclusions pertinent to the current discussion. First, lesions of the caudate nucleus both bilateral and unilateral, may result in abulia, or in rarer cases, disinhibited behaviors. Second, lesions of the caudate nucleus infrequently cause motor disorders. These conclusions were in direct contrast to the authors' findings regarding the other basal ganglia structures they examined, which were more related to motor difficulties following

injury. The importance of this work lies in the finding that lesions to the caudate nucleus were more associated with behavioral disinhibition than overt motor activity.

While lesion studies and case analysis serve to link specific brain structures to their associated behaviors, other brain research has focused on examining functional brain systems. Most researchers would agree that the brain functions as a unit, with communication between brain regions attributed to neurotransmitter pathways. Damage to a particular structure, therefore, not only results in diminished functioning of that brain region, but also serves to impact on other brain areas in communication with that structure via neurotransmitters. Much of our understanding about brain functioning stems from studies which examine this connection between structural variation and metabolic dysregulation.

Neurotransmitter Research

A large portion of research that has provided support for a neuroanatomical model of ADHD comes from the study of neurotransmitters. One group of neurotransmitters that has been studied extensively through animal models is the catacholamines. Catacholamines are produced in the brain by the precursor amino acid 1-tyrosine, which is obtained from our diet and delivered to the brain in the blood supply. Two types of catacholamines, the neurotransmitters dopamine (DA) and norepinephrine (NE) are produced when certain enzymes act upon tyrosine. These neurotransmitters are activated when released into the synaptic cleft formed between two communicating neurons and are inactivated by their reuptake into the original (releasing) neuron or through their metabolism. The catacholamine are metabolized by two enzymes, monamine oxidase

(MAO) and catechol-o-methyltransferase (COMT). Therefore, problems in the production of catecholamine or in their inactivation may result in the inability of neurons to communicate normally.

The catacholamines are the neurotransmitters responsible for controlling attentional processes. Specifically, they have been found to play a role in motivation and motor behaviors such as activity level, restlessness, and responsivity (Hynd, et al., 1991). In fact the drugs typically used to treat ADHD serve to increase the amount of catacholine available, which works to help inhibit certain behaviors. The role of stimulant medication (e.g., Ritalin, Cylert) on the brain mechanisms of children with ADHD appears to influence the motor readiness-impulse control systems (Lou, et al., 1989). Stimulants facilitate the synthesis and release of catacholamine at the synapse and block their reuptake (Weiss & Hechtman, 1993). The behavioral result of the stimulant medication is to reduce the excessive motor activity and impulsivity while improving attentional processes.

Research examining the effects of stimulants in animals have concluded that the behavioral effects of these drugs are mediated by forebrain dopamine systems, in particular projections to the nucleus accumbens and the structures of the ventral striatum, which contain the caudate nucleus. Robbins, Jones, & Sahakian, (1989) found that rearing rats in isolation produced a behavioral syndrome of hyperactivity, which persisted into adulthood. These rats exhibited enhanced reactivity to external stimuli, enhanced exploration of the environment, made more errors on a spatial memory task, and were slower than controls on learning and attention tasks. These rats were found to display

enhanced responsiveness to stimulant medication, indicated by increased stereotyped behavior (e.g., licking, biting, grooming). They determined that these rats had diminished concentrations of dopamine, particularly in the striatum. Seiden, Miller, & Heffner (1989) reviewed the research regarding neurotransmitters implicated in ADHD and concluded that dopamine and norepinephrine supplies may be decreased in children with ADHD.

Roeltgen and Schneider (1991) administered chronic low doses of methyphenyl-1,2,3,6-tetrahydropyridine (MPTP) to monkeys and produced behavioral deficits similar to those seen in children with ADHD. MPTP is a toxin shown to damage the caudate nuclei. During delayed response and delayed alternation tasks, the monkeys exhibited difficulty responding, impersistance, frustration, need for redirection, irritability, restlessness, and fidgeting. An additional task requiring the use of planning and organizing strategies was found to be more difficult for the monkeys exposed to MPTP. Postmortem studies (Schneider, 1990) of these monkeys produced evidence for depleted dopamine and norepinephrine in the head of the caudate and putamen. These two studies provide empirical support for the role of neurotransmitter functioning in producing the behaviors seen in ADHD. More importantly, they link the site for the neurotransmitter activity to the head of the caudate nucleus.

The caudate has also been implicated in working memory functioning. Using a radial arm maze task, Packard and White (1990) found that lesions of the caudate neucleus in rats impaired the acquisition of reference memory but did not affect their working memory. Lesions of premotor cortex in macaque monkeys produced monkeys

who were unable to inhibit their responses in a structured paradigm and behaved in a repetitive and impulsive manner (Rizzolatti, et al., 1983). The learning of adaptive behaviors has also been implicated as being influenced by striatal interneurons, specifically dependent upon dopamine synthesis (Graybiel, Aosaki, Flaherty, & Kimura, 1994). The firing of striatal neurons in monkeys was found to increase significantly during a learning task which resulted in a food reward.

In summary, the research examining neurotransmitter functioning in ADHD provides evidence that two types of catacholamines, dopamine and norepinephrine, seem to play a role in the behavioral presentation of ADHD. Specifically, motor activity and impulsivity appear to be regulated by these neurotransmitters. Research suggests that these neurotransmitters may be depleted in individuals with ADHD, particularly in the frontal and caudate-putamen areas. While research into the significance of neurotransmitter activity continues, neuroimaging studies examining brain structures in vivo have also emerged. This type of research builds on lesion studies, case studies, and metabolic studies by creating a forum to view structural differences without using invasive techniques. This is particularly relevant to disorders which may be attributed to developmental variations in brain structures (e.g., dyslexia, ADHD), because hypotheses which could previously only be postulated can now be empirically studied.

Neuroimaging and Behavioral Disorders

Imaging techniques have already supported a neuroanatomical basis for other developmental disorders, such as dyslexia (Galaburda, 1985; Galaburda, 1995; Hynd, et al., 1990, 1995). However, imaging work on children with ADHD has only recently

begun to provide some support for a neurological basis for ADHD. In a study by Shaywitz, Shaywitz, Byrne, Cohen, & Rothman (1983) computed tomography (CT) scans comparing children with ADHD to normal controls, indicated that there were neurological abnormalities in nearly 30% of the ADHD cases. However, a follow-up investigation (Harcherak, Cohen, Ort, Paul, Shaywitz, Volkmar, Rothman, & Leckman, 1985*)* failed to support this finding and argued that CT scans were indistinguishable between ADHD and normal groups.

Another study using positron emission tomography (PET) found that in a group of adults with residual type ADD, there was decreased glucose utilization in the frontal areas, but increased utilization in the posterior medial orbital areas (Zametkin, Nordahl, Gross, King, Semple, Rumsey, Hamburger, & Cohen, 1990). This group completed a series of PET studies on these adults with residual ADHD and found decreased glucose utilization throughout the whole brain, but specifically in the frontal lobe (orbital regions and right greater than left). The subjects were also given a continuous performance task to measure sustained attention. Increased rates of glucose metabolism, which indicate brain activity, was lower in the adults with ADHD than in the control subjects during this task. The most significant discrepancies occurred in the bilateral premotor and superior frontal cortices, cingulate, right thalamus, caudate, and hippocampus.

In a follow-up study, this group used the same methodology on a group of unmedicated adolescents with ADHD (Zametkin, Liebenauer, Fitzgerald, King, Minkunas, Herscovitch, Yamada, & Cohen, 1993). Their findings supported their earlier work with adults in that the normalized metabolic rates were lower in the ADHD

subjects' left thalamus, right temporal region, and hippocampus. Importantly, metabolic rates in the left frontal region were significantly correlated with measures of symptom severity.

However, a Danish study of 13 children with learning and attention problems (Lou et al., 1984) indicates that administration of methylphenidate (Ritalin) increased perfusion in the midbrain and basal ganglia while decreasing perfusion in cortical areas. It was concluded that the children with ADHD had lower metabolic rates in the region of the caudate, specifically the right striatum. In later research with a group of six subjects with ADHD, the authors (Lou, et al., 1989) demonstrated hypoperfusion of the right striatum, and relative hypoperfusion of the left primary auditory, sensorimotor, and bilateral occipital regions. Importantly, when methyphenidate was administered to these subjects, the perfusion increased significantly in the left but not the right striatum and in bilateral posterior periventricular regions This finding suggests that there may be a dysfunction of the right striatum in the ability to stop uptake of dopamine.

More recently, studies using magnetic resonance imaging (MRI) have begun to emerge specifically investigating neurological relationships in childhood disorders such as ADHD. Hynd, Semrud-Clikeman, Lorys, Novey, & Eliopulos (1990) produced an often cited study that examined the brain morphology of developmental dyslexics, children with ADHD, and normal controls. Using saggital and axial MRI scans, the authors examined the width and area of anterior (frontal) and posterior regions, insular regions, and planum temporale. Significant differences were found in the anterior width measurements, with the dyslexic and children with ADHD displaying smaller anterior

cortexes bilaterally than the normal control children who demonstrated the normal right>left (R>L) asymmetry. When this difference was examined further, it was discovered that this finding was the result of significantly smaller widths in the right anterior region. Insular region and plana temporale measurements did not differ significantly between the ADHD and normal control children, although the dyslexic group did show significant differences. Where normal children display a natural pattern of asymmetry in the anterior region (L<R), ADHD and dyslexic children either had a lack of asymmetry or reversed asymmetry. This finding suggests that subcortical frontal structures, such as the caudate nucleus, may also show atypical asymmetry in size, likely due to some influence, possibly genetic, in neurological development and associated variation.

Hynd, Semrud-Clikeman, Lorys, Novey, Eliopulos, & Lyytinen (1991) expanded upon this earlier work by examining a subcortical structure, the corpus callosum, on MRI. Their main finding showed that areas of the corpus callosum in seven children with ADHD was smaller when compared to that of ten normal controls. The authors segmented the corpus callosum on a midsagittal cross-sectional MRI scan into five equal regions and performed comparisons between the two groups on each of these divisions. The genu, splenium, and region anterior to the splenium were found to be significantly smaller in size among the ADHD group. These findings are important for supporting a neurodevelopmental theory of ADHD. First, the size of the corpus callosum appears to be regulated by genetic factors. Secondly, these areas of the corpus callosum have major connections with other regions implicated in this disorder. The genu is known to be

comprised of fiber connections serving the premotor, orbitofrontal, and prefrontal regions, while the splenium houses interconnections pertaining to the occipital and portions of the internal capsule. Deficits in motor regulation, motor persistence, and inhibition that have been associated with frontal systems may reflect dysfunction in the neural pathways which influence these functions (Hynd & Willis, 1988).

A second group of researchers (Giedd, Castellanos, Casey, Kozurch, King, Hamburger, & Rapoport, 1994) replicated this study with a larger group and more powerful scanner (GE 1.5 Tesla), and thinner slices (1.5mm). Subjects included 18 ADHD males and 18 normal controls who were matched for age, weight, height, handedness, and developmental stage. A number of cognitive, attentional and behavioral measures were also administered. Measurements of the corpus callosum were made in a total of seven sections, and high interrater reliabilities were reported. On the cognitive measures, the groups differed on the vocabulary and block design subtests of the WISC-R, with the ADHD group having lower scores than the comparison children. There were no group differences on the attentional measures. Behavioral data found that the ADHD group scored significantly higher on the conduct and impulsivity/hyperactivty factors of the Conners parent questionnaire. The ADHD group differed significantly in measurements of the rostrum and rostral body regions of the corpus callosum as their measurements were significantly smaller than the normal controls. Most importantly, the smaller areas correlated with higher ratings of impulsivity/hyperactivity on the parent and teacher Conners questionnaire. This study differed from the work of Hynd, et al., (1991)

in that only the anterior regions of the corpus callosum were significantly smaller in the ADHD children. However, the difference in the divisions of the corpus callosum (five v. seven) may clear up some of this discrepancy, as the Hynd, et al., study measured larger areas. The rostrum, genu, and portions of the rostral body delineated in the Giedd, et al., (1994) study correspond to the genu as named by Hynd, et al., (1991). The importance of both of these studies pertaining to the current hypothesis is that both studies found significant differences in the frontal regions of the corpus callosum that also contain caudate/orbital prefrontal projections.

There have also been MRI studies that have focused specifically on finding group differences in the size of the caudate nucleus. Hynd, Hern, Novey, Eliopulos, Marshall, Gonzalez, & Voeller (1993) examined MRI scans in 11 children with ADHD and 11 normal controls and compared the size of the head of the caudate nucleus. The children were diagnosed with ADHD using DSM-III-R criteria and were screened for neurological conditions. The MRI protocol involved a 0.6-T Health Images scanner on which sequential T1 sagittal and axial planes were examined after proper head alignment was confirmed. The measurements were taken from a midaxial scan where the anterior horn of the lateral ventricles and the head of the caudate nucleus could be visualized. Prior to their analyses, it was determined that there were no statistical differences between groups that could be the result of age, handedness, and overall brain size. The groups differed significantly in intellectual ability (normal controls > ADHD), codiagnoses (normal controls < ADHD), and behavioral ratings on the Externalizing Scale of the Achenbach Child Behavior Checklist (Achenbach, 1983). Children were classified into one of three

categories based upon laterality (left/right): L>R, L<R, or L=R. Using this classification, 72.7% of the control children had a L>R pattern while 63.6% of the ADHD children had a L<R pattern. This finding was statistically significant. A significant interaction effect for group by asymmetry was attributed to a relatively smaller left caudate nucleus in the children with ADHD. Further exploratory analyses were conducted to examine the relationship between handedness (all subjects were right-handed) and gender (8/11 ADHD subjects were male), but no significant findings for these variables were found. The authors concluded that the L<R asymmetry evident in the children with ADHD implicated the caudate-striatal region in this disorder. Similar findings of L>R asymmetry have been documented in other samples of normal adults and children (Filipek, et al. 1994; Caviness, et al. 1997).

Further support for developmental abnormalities in the frontal-striatal pathways were found by Castellanos, Giedd, Eckburg, Marsh, Vaituzis, Kaysen, Hamburger, & Rapoport (1994). These researchers, however, obtained contradictory findings to Hynd, et al. (1993). Castellanos, et al. (1994) compared the brains of 50 males with ADHD (aged 6-19) and 48 normal controls by examining the caudate and total brain volumes. ADHD subjects were diagnosed using DSM III and DSM-III-R criteria and were screened for neurological and psychiatric conditions, with the exception of conduct disorder and oppositional defiant disorder. The normal controls were matched for age as well as body size. A majority of both groups (>85%) were right-handed. The subjects were scanned with a GE 1.5 Tesla Signa scanner and head alignment was standardized. Volumetric measurements were gathered on T1-weighted coronal images (2.0mm slice).

Area measurements were obtained on the head and body of the caudate nuclei by manually outlining these areas on alternating 2.0mm slices where they were visible. These area measurements were then multiplied by slice thicknesses to derive volumes. The posterior region of the caudate head was delineated as the coronal slice containing the interventricular foramina. The sum of the caudate head and body was obtained for each hemisphere and right-left asymmetry was defined by the formula (R-L)/[(R+L)/2]x100 so that a positive score would indicate right greater than left caudate volume. It was found that the mean total brain volume for the normal controls was significantly greater than that of the ADHD subjects. As one would expect, total right and left volume correlated significantly with caudate volume (at p=.0001 for each). Looking specifically at asymmetry between right and left caudate volumes, the normal controls had a significant R>L asymmetry while the ADHD group did not have significant asymmetry. Post hoc testing confirmed that for the normal controls, the right caudate was significantly larger than the left (p=.05) while they did not differ significantly for the ADHD group. A developmental trend was discovered when the researchers divided the large age range into four smaller age ranges. When they conducted their analysis of variance according to the smaller age groups, they found that the caudate volumes decreased with age for the normal controls, but did not decrease for the ADHD children. The authors hypothesized that this developmental trend may be explained by synaptic pruning which occurs more efficiently in normal brains. Overall, the authors found support for a R>L asymmetry of the caudate in normal controls (aged 6-19). This finding contradicted the results of Hynd, et al. (1993) which found L>R asymmetry in

their normal controls (aged 8-12). Differences in sample size, strength of the scanner,

hemispheric regions found the ADHD group had significantly smaller hemispheres in this region than the controls, which was the result of significantly smaller right anterior-superior regions. The smaller right regions produced a more symmetric anterior-superior volumes, compared to controls who had asymmetrical (L>R) volumes. Bilaterally, the anterior-inferior hemispheric regions (which contain the caudate head and portions of the basal ganglia) were significantly smaller in the ADHD group than in controls. When the total volumes of the caudate (head+tail) were compared, the ADHD group had significantly smaller caudate nuclei. Post hoc analyses indicated that this was the result of a significantly smaller left caudate, which resulted in symmetric caudate volumes for the ADHD group and L>R asymmetry for normal controls, similar to the results reported by Hynd, et al. (1993). Sixty-seven percent of the normal controls evidenced this pattern of asymmetry, compared to 27% of the ADHD group.

When just the head of the caudate was examined, similar differences in volumes were found. The ADHD subjects had significantly smaller total volumes of the right and left caudate head. Post hoc analyses localized this difference to a significantly smaller left caudate head, which resulted in an increased caudate symmetry. No differences were found in the measurements of the caudate tail. Some exploratory analyses were conducted to compare the impact of medication (e.g., responders versus nonresponders) to volumetric measures. In the controls, the right caudate was smaller than the left, in the stimulant nonresponders, the right caudate was larger than the left (reversed asymmetry), and in the stimulant responders, the caudate head volumes were symmetrical. The authors concluded from these results that a disturbance in neurodevelopment, particularly

in the right hemisphere, may occur in children with ADHD. Their findings also support a neurological basis for the existence of two of Posner and Petersen's attentional networks, the alerting arousal and executive networks.

Most recently, a team of researchers in Spain have examined the caudate nucleus in a group of adolescents with ADHD. Mataro, Garcia-Sanchez, Junque, Estevez-Gonzalez, and Pujol (1997) compared eleven adolescents diagnosed with ADHD (14.6±.05) and nineteen normal controls (14.8±.7). All subjects were screened for average intelligence and absence of brain damage. Transversal (axial) images were obtained on a GE 1.5 Tesla scanner (15 continguous 5mm slices, with interslice gaps of 2.5mm). Anatomical reference points were obtained on a sagittal scan. Area measurements for the head of the caudate nucleus and total brain were performed on a single mid-transversal slice. A number of neuropsychological and behavioral measures were also obtained for each subject. The authors assessed the domains of attention (Continuous Performance Test[CPT], Paced Auditory Scales of Attention Test[PASAT], Brown-Peterson distractor paradigm), frontal lobe functions (Wisconsin Card Sorting Test[WCST], Tower of Hanoi, Trail Making Test, and verbal fluency measures), memory (Auditory Verbal Learning Test[AVLT], Rey-Osterrieth Complex Figure), perception, intelligence (Weschler Adult Intelligence Scale[WAIS]), and behavior (Conners Teachers Rating Scale). Results of the area measurements found that the ADHD group had a significantly smaller right caudate nucleus when compared to controls. No significant differences in patterns of asymmetry were found. An examination of group means, however, showed a pattern of L>R asymmetry in the head of the caudate nucleus in the

normal control group, while the ADHD group displayed a trend towards a R>L asymmetry. No significant differences were found between the male and female subjects. On the neuropsychological data, several significant findings were reported. After controlling for the effects of IQ, the ADHD group performed significantly poorer than controls on two of the attentional tasks (PASAT and CPT). Correlations between the morphological data and the neuropsychological and behavioral measures were also conducted. Among the normal controls, the area of the right caudate correlated significantly with scales on the CPT and the Conners Teachers Rating Scale. Larger area values were associated with poorer performance on the CPT and higher ratings on the Conners. The same trend emerged for the area values of the left caudate nucleus for the normals. The only significant correlation for the ADHD group was an association between a larger left caudate and longer time to solve the Tower of Hanoi. The authors interpreted their findings to suggest a bilateral frontal-striatal dysfunction involved in ADHD, which is more pronounced for the right hemisphere. Although they did not find significant patterns of asymmetry among their subjects, comparison of area values supports the R>L asymmetry in ADHD discussed in Hynd, et al. (1993).

Statement of the Problem

Given the neuroanatomical, neurochemical, and neuropsychological evidence which links the caudate nucleus to motor excesses and impulsivity, it is hypothesized that a morphological difference is evident in the brains of children identified with ADHD. Specifically, the hypothesis that children with ADHD display a smaller head of the caudate nucleus when compared to normal controls and a clinical comparison group was

explored by this study. The current study also investigated the direction of asymmetry of the caudate nucleus, to address the discrepant findings in the existing research (e.g., L<R versus R<L). To address the question about morphological differences in the caudate among groups, the following hypotheses were investigated:

1. Children with ADHD do not differ from normal controls and a clinical group (reading disabled) in the size (e.g., area, volume) of the head of the caudate nucleus.

2. The children with ADHD do not display a different pattern of asymmetry in the caudate nucleus (for area and volume) when compared to the other groups.

Additionally, the relationship between structural variations in the head of the caudate and the behaviors associated with ADHD (e.g., impulsivity, hyperactivity) were examined. This correlation is anticipated because deficits in impulse control and executive functioning characterize children with ADHD and not normal or reading disabled children. Although comparisons between caudate morphology and behavioral data have been examined in adults and adolescents, this type of analyses has yet to be conducted with children. The following hypotheses to explore this aspect of the study are stated below:

3. The variations in caudate morphology (e.g., area, volume) are not related to performance on measures of behavioral inhibition and executive functioning for the total sample or the ADHD group.

4. The magnitude of the measurements for the caudate nucleus (e.g., area, volume) will not display any relationship to the direction of any existing correlations. Specifically, higher ratings of behaviors of disinhibition and motor over-activity (e.g., hyperactivity, impulsivity, externalizing behaviors) will not be associated with smaller caudate size. Lower ratings of performance on executive functioning will not be correlated with smaller caudate size.

CHAPTER III

METHOD

Participants

The subjects in this study were selected from consecutive referrals to the Center for Clinical and Developmental Neuropsychology at the University of Georgia. These children were participants in an ongoing research project funded by the National Institutes of Health (NIH). Referrals to the clinic were made by physicians, schools, local organizations, and families. The children ranged in age from eight to twelve years old. Subjects were excluded for neurological disorders (e.g., epilepsy, head injury) and borderline cognitive ability (WISC-III, FSIQ<85) (Wechsler, 1991). Children were not on medication at the time of assessment.

Out of the total sample, only those children who had clear (MRI) brain images available were selected for this study. Fifty-four children were obtained from the larger database. There were 20 children diagnosed with ADHD (14 males, 6 females), 22 children with reading disability (14 males, 8 females), and 12 normal control children (5 males, 7 females). The subjects with reading disability were included in this study as a clinical comparison group. Among the subjects diagnosed with ADHD, there were 6 identified as Predominantly Inattentive Type and 14 identified as Combined Type.

Procedure

Written informed consent was obtained from parents and oral assent was obtained from all subjects. Each child was given a comprehensive neuropsychological evaluation which consisted of measures of cognitive, linguistic, visuospatial, visual-motor, achievement, behavioral, and neuropsychological abilities. The children were also administered a brain imaging protocol using magnetic resonance imaging (MRI) conducted at Athens Magnetic Imaging, Athens, Georgia.

Diagnostic Protocol

Diagnoses of reading disability and ADHD were made according to pre-specified criteria. Diagnosis was made by either a post doctoral fellow or advanced psychology graduate student and confirmed by a licensed psychologist.

A diagnosis of ADHD was made using criteria in the Diagnostic and Statistical Manual -Fourth Edition (DSM-IV, APA 1994). Parents and teachers completed the following behavior rating scales: Behavior Assessment System for Children (BASC; Reynolds & Kamphaus, 1993), Child Behavior Checklist (CBCL; Achenbach & Edelbrock, 1983), and the SNAP Checklist (Atkins, Pelham & Licht, 1985). Parents also participated in a structured interview, a version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS; Puig-Antich & Chambers, 1978), and completed a DSM-IV ADHD checklist. Final diagnosis was made on the basis of clinical judgment of the licensed psychologist, interview data, and behavior reports.

This diagnostic procedure with these subjects was reported to be reliable in a previous study (Morgan, Hynd, Riccio, & Hall, 1996).

The children diagnosed with reading disability (RD) had a 20-point discrepancy between scores on both word recognition and reading comprehension tasks and cognitive ability (FSIQ on the WISC-III). Cognitive ability was measured using the Wechsler Intelligence Scale for Children, Third Edition (WISC-III), which is an individually administered, norm-referenced intelligence test. The split-half reliability coefficient for WISC-III Full-Scale IQ is .96 and the test-retest reliability is .94. Reading tasks included the Wide Range Achievement Test-3 (WRAT-3, Wilkinson, 1993) and the Word Attack and Passage Comprehension subtests from the Woodcock Reading Mastery Test-Revised (WRMT-R, Woodcock, 1987). Both of these measures are individually administered, norm-referenced tests of achievement. On the Word Attack subtest, subjects are asked to read nonsense words. The Passage Comprehension subtest requires subjects to read a short passage to themselves and supply a key missing word. All of these reading measures have acceptable reliability. The test-retest reliability for the reading subtest of the WRAT-3 ranges from .96 to .98. The split-half reliability for WRMT-R Word Attack ranges from .89 to .95 and for Passage Comprehension ranges from .73 to .96 for children 8-12 years of age. The mean reading scores on the WRAT-3 for the reading disabled children was 77.4 (standard deviation 11.1) and mean Full Scale IQ was measured to be 101.7 (standard deviation 15.4). Children with a secondary diagnosis of ADHD were excluded from the RD group, but these subjects may have had some other secondary diagnosis (e.g., specific language impairment, anxiety disorder).

Children classified as normal controls were recruited from the community as children who had no learning or behavior problems. Those children identified as normal controls were not found to have any diagnosis resulting from the neuropsychological testing and the parent interview. There was no reported history of learning problems, achievement difficulties, attentional problems, and other social/emotional problems for these children.

Neuropsychological Variables

A number of the behavioral and neuropsychological variables are used in the current study. These include: Rapid Alternating Stimulus, Wisconsin Card Sorting Test, WISC-III Coding, Edinburgh Handedness Inventory, BASC, CBCL, and the SNAP.

The neuropsychological tasks were included based upon literature indicating that children with ADHD have difficulties with executive functioning and impulsivity, behaviors which are associated with frontal-striatal systems. The Rapid Alternating Stimulus (RAS; Denckla & Rudel, 1976) is a clinical research measure of executive functioning where children are required to rapidly name changing visual stimuli. This skill taps both selective attention and response inhibition, which would be impaired in children with ADHD. Another measure of executive functioning, the Wisconsin Card Sorting Test (WCST; Heaton, 1981) assesses the child's ability to learn how to respond to changing stimuli with the correct response. Neuropsychological literature has found impairment in card sorting tasks linked to the frontal lobes (Spreen, Risser, & Edgall, 1995). The ability to persevere during the task (Failure to Maintain Set) as well as the number of correct "sets" the child obtains (Number of Categories) are two standardized

scores that can be obtained from the WCST. Inter-rater reliability for the WCST was found to range between .89 to 1.0 (Heaton, 1981). The Coding subtest from the WISC-III was included as a measure of motor persistence and selective attention (Lezak, 1995). A similar task, the Digit Symbol subtest of the WAIS-R (Wechsler, 1981) was found to be sensitive in adults with Huntington's disease (Strauss & Brandt, 1984) while poor performance on another version of this test, the Symbol Digit Modalities Test (SDMT) was found to be correlated with evidence of caudate atrophy in Huntington patients (Starkstein, Brandt, Folstein, et al., 1988). It is anticipated that the children with ADHD will demonstrate impaired performance on these measures of executive functioning compared to the RD and normal control groups. Lastly, the Edinburgh Handedness Inventory (Oldfield, 1971) was administered as a measure of laterality, or hand dominance. Children performed a series of ten tasks with their preferred and non-preferred hands. Positive scores indicate right hand dominance, while negative scores indicate left hand dominance. Reliability of the Edinburgh was measured by Raczkowski, Kalat, & Nebes (1974) and agreement between three trials ranged between 89-100% on six items.

Behavioral Variables

Specific behavioral variables were selected from the database to examine behavioral inhibition, motor activity, attention, and impulsivity. These included from the BASC-PRS (Parent Rating Scale) the Externalizing Problems Composite, Hyperactivity scale, and Attention Problems scale. The identical scales were taken from the BASC-TRS (Teacher Rating Scale). The BASC-PRS is comprised of 12 scales related to

childhood behavior problems and adaptive behaviors. It has a large normative sample (N = 2084) that was stratified to match U.S. Census data. Reliability coefficients for the subscales and composite scores generally fall in the range of .80 or higher, with the lowest coefficient a .67. The BASC-TRS is a teacher version that includes 14 scales (the additional two are related to school behaviors). Reliability coefficients (internal consistency and test-retest) generally range in the .80s. Lastly, the Impulsivity scale from the parent and teacher SNAP was used in this study. The behaviors from the SNAP checklist are similar to those identified in the DSM-IV as associated with impulsivity.

MRI Protocol

MRI scans were obtained using a 0.6 Tesla Heath Images (Atlanta, GA) scanner. The protocol included fifteen gapless, three-dimensional, 3.1 mm sagittal planes [TR=51, TE=10 (prior to 9/23/95) or TE=13 (after 9/23/95). The scans were read by a board certified neurologist and all subjects were determined to have normal scans. Head position was monitored by using "scout" scans to ensure that standardized head alignment was obtained.

Brain measurements were made using a Health Images workstation located at the University of Georgia with software designed for viewing MRI images obtained from the National Institute of Health (NIH). All measurements will be made on the axial plane. Some studies examining the caudate have used sagittal or coronal planes (Castellanos, et al., 1994; Filipek, et al., 1997), but others (Hynd, et al., 1993; Mataro, et al., 1997) using transverse (axial) plane measurements suggests that this plane may provide the most reliable view of the head of the caudate nucleus (see Figures 2 and 3). Additionally, these

other studies included the body and tail of the caudate, which may involve a greater degree of judgment error when differentiating the caudate from surrounding tissue. The procedure used for defining the head of the caudate nucleus was described by Hynd, et al., (1993), who used other brain structures (e.g., corpus callosum, lateral ventricles) to define the boundaries of the caudate. The head of the caudate nucleus is visible in approximately three axial scans, and area measurements will be made on each of these scans so that

volume can be estimated. The calculation for determining volume, where "x" = area measurement and numbers signify slice, was $[x_1 (3.1) + x_2(3.1) + x_3(3.1)]$. The imaging software calculates the area of the defined area (interior to traced borders) automatically. Measurements of each subject's right and left caudate nucleus were gathered.

The measurement protocol also involved measuring the entire brain on a midpoint scan to obtain an estimate of total brain size. The midpoint scan was identified as being the scan which bisected the caudate nucleus. The area measured was the brain region superior to the cerebellum, pons, and medulla. The scan used for measuring total brain size was the same scan that provided the "best view" of the caudate nucleus. Total brain size measurements were collected so that any differences between groups in overall brain size could be compared. A significant difference would indicate that brain size should be used as a covariate in the analysis.

Classifications of symmetry/asymmetry were made for each subject based upon caudate nucleus area and volume measurements. Interhemispheric coefficients were calculated according to the formula [(R - L)/[(R + L)/2 X 100] as described by

Castellanos, et al., 1994. According to this calculation, positive values indiate rightward asymmetry (R > L) while negative values signify leftward asymmetry (L > R).

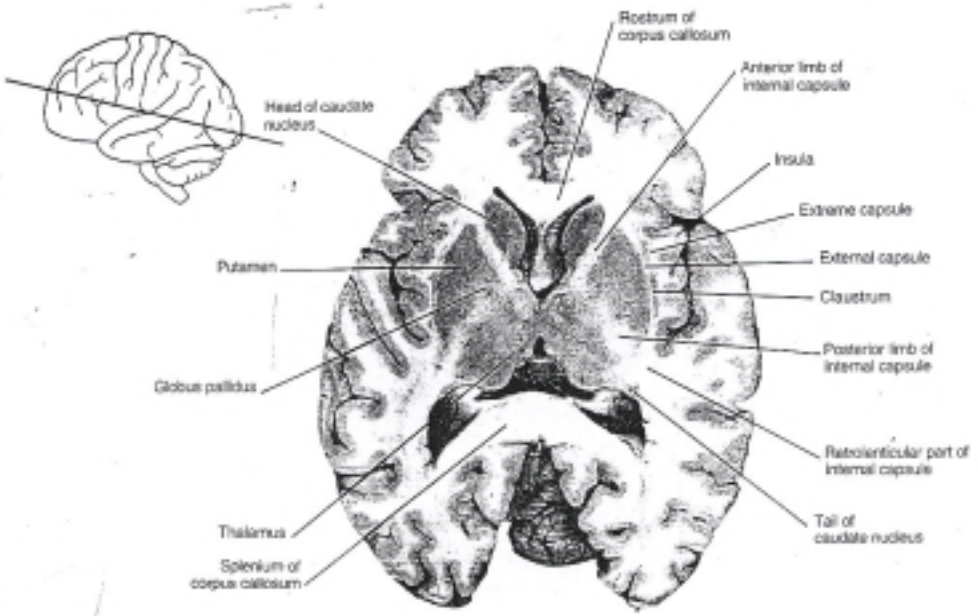

Figure 2. Horizontal tissue slice of the head of the caudate nucleus (Crossman & Neary, 1995)

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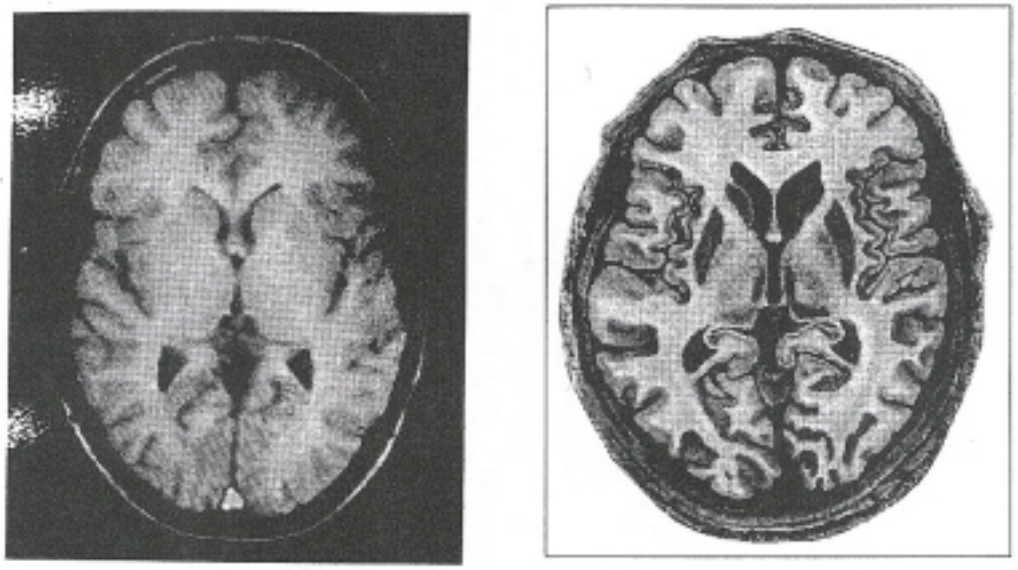

Figure 3. T1 and T2 magnetic resonance image (MRI) indicating head of caudate nucleus on a horizontal plane (Mai, Assheuer, & Paxinos, 1996)

Figure 3. T1 and T2 magnetic resonance image (MRI) indicating head of caudate nucleus on a horizontal plane (Mai, Assheuer, & Paxinos, 1996)

Coefficients that fell between $\pm$ 0.10 were classified as symmetrical (L = R). This procedure has been used in other research (Hynd, et al., 1990) interested in asymmetry patterns.

Interrater reliability estimates were calculated from two independent raters (author, GWH) trained in the measurement protocol. Both raters were blind to diagnostic category. Ten scans were randomly selected for reliability purposes, and twenty measurements (e.g., right and left hemisphere) were made at two different times. Both caudate and total brain size measurements were collected. Estimates of interrater reliability were as follows: Left caudate area (r = .97), Right caudate area (r = .93), Total Brain area (r = .92).

Intrarater reliability estimates were then calculated on ten randomly selected scans with diagnostic category unknown to the author. The final intrarater reliabilities were as follows: Left caudate area (r = .94), Right caudate area (r = .92), and Total Brain area (r = .97). All subsequent brain measurements were made by the author following the reliability study. The subject's diagnostic category was unknown to the author at the time of measurement.

A qualitative rating was given to each measurement for all subjects. Each area measurement was rated for Accuracy of Measurement and Quality of Image. Accuracy was rated on a 5-point Likert scale defined as follows: 1 = poor accuracy, 2 = minimal accuracy, 3 = acceptable accuracy, 4 = fair accuracy, and 5 = good accuracy. Accuracy was defined as how confident the rater was about the accuracy of the measurement. Quality was rated on a 5-point Likert scale defined as follows: 1 = poor clarity, 2 =

minimal clarity, 3 = acceptable clarity, 4 = fair clarity, and 5 = good clarity. Quality was defined as the degree of clarity of image quality on the MRI scan. These ratings were gathered to explore the possibility that measurement error and/or image quality differed between groups.

Analyses

A series of one-way analyses of variance (ANOVA) were used to determine if the three groups differed significantly on age, handedness, gender, total brain size, and FSIQ. These variables are routinely reported as control variables in brain imaging literature, given the impact of each on structural measurement. Significant findings would be used as covariates in subsequent analyses. Therefore, any group differences in caudate size could be attributed to real morphological differences rather than one of these other variables.

Analyses of the qualitative date (Accuracy, Quality) were conducted using the Friedman test, a nonparametric procedure used for ranked data, to look for significant differences between measures of accuracy and quality for right and left caudate nucleus. This measure was followed by a series of one-way ANOVAs to investigate whether groups differed in their Accuracy and Quality ratings.

Following these analyses, a series of one-way ANOVAs were run to see if there were group (ADHD, RD, and normals) differences in (1) caudate area for right and left hemispheres, and (2) caudate volume for the right and left hemispheres. Significance level for group differences was set at the $p<.05$ level. Following the ANOVAs, a series of t-tests for dependent samples was performed for each pair of measurements within

each group. For example, two comparisons of means (caudate left and right area, caudate left and right volume) were run for each group (normal controls, RD, ADHD). Significance level for differences was set at $p < .05$.

Chi square analysis (3 x 3 matrix) was used to examine differences in group symmetry/asymmetry patterns. Examination of frequencies within each group provided further analysis of the directionality of asymmetry patterns. Significance level for differences was set at $p < .05$.

Pearson's correlational analyses were run between caudate size (area, volume) for each hemisphere and each of the cognitive/behavioral variables of interest. These variables include the following: RAS Error raw score, WCST Failure to Maintain Set, WCST Number of Categories, WISC-III Coding, BASC-PRS Hyperactivity Scale, BASC-PRS Attention Problems Scale, BASC-PRS Externalizing Problems Composite, BASC-TRS Hyperactivity Scale, BASC-TRS Attention Problems Scale, BASC-TRS Externalizing Problems Composite, Parent SNAP Impulsiveness scale, Teacher SNAP Impulsiveness scale. As mentioned above, these variables were selected to explore the hypotheses that problems with behavioral disinhibition and control are associated with ADHD. The significance level was set at $p<.05$ to provide the greatest chance that despite the small group sizes, meaningful relationships were revealed.

The results of the analyses are presented in the following chapter along with supporting table. A discussion of the results will follow.

CHAPTER IV

RESULTS

The results in this chapter were gathered to address the hypotheses of this research study. First, it was anticipated that the ADHD group would differ from the normal controls and a clinical group (reading disabled subjects) in measurements of the head of the caudate nucleus. Exploratory analyses were conducted to determine if confidence ratings (e.g., accuracy of measurement, quality of scan) resulted in any group differences. Secondly, it was assumed that these groups would also differ in the direction of asymmetry of the size of the caudate nucleus (e.g., right greater than left, left greater than right, or symmetry). Finally, correlational analyses were conducted to examine the hypotheses that caudate size is associated with behavioral variables, specifically performance on executive functioning measures and behavior ratings (e.g., hyperactivity, impulsiveness, attention problems, and externalizing behaviors). Before these results can be reported, descriptive statistics for each group are provided.

Data Analyses

Descriptive Statistics

As discussed in the Methods chapter, the three groups were compared on measures of age, handedness, gender, cognitive ability, and total brain size. Specific measures of these variables included the Edinburgh Handedness Inventory, Wechsler Intelligence Scale for Children, Third Edition (WISC-III) Full Scale IQ, and total brain size (cm^2). Full scale IQ was unavailable for one RD subject and one ADHD subject.

Handedness was not assessed for two normal controls and one RD subject. Group means and standard deviations for these variables are presented in Table 1. There were no significant group differences on age [F = .05, $p < .95$], on cognitive ability [F = 2.22, $p < .12$], handedness [F = 1.13, $p < .33$], gender [F = 2.24, $p < .12$], or total brain size [F = .85, $p < .43$]. Given the absence of any significant group differences, no covariates were used in the subsequent analyses.

Confidence Measures

Exploratory analyses to compare confidence ratings for each of the measurements was conducted to determine if groups differed on these ratings. At the time of each measurement, the author used a Likert scale to rate each measurement on (1) accuracy of measurement and (2) quality of image on scan. Means and standard deviations for each rating by group is displayed in Table 2. A nonparametric test for related samples (Friedman test) was used to compare the accuracy and quality ratings for the total sample. This test was used to test the hypothesis that there are no differences between ratings for the right and left caudate area measurements. This method is suggested when the same rater produces rankings on some variable (SPSS 7.5, 1997). Comparisons of the accuracy ratings for right and left caudate area was significantly different for the total sample [χ^2= 3.77, $p < .05$]. There were no significant differences between the quality ratings for the right and left caudate area [$\chi^2 = .000$, $p < 1.0$]. When groups were compared to one another, there were no group differences for accuracy of right caudate nucleus measure [F = 2.03, $p < .141$], quality of right caudate nucleus images [F = 2.29, $p < .112$], or quality of left caudate nucleus images [F = 2.29, $p < .112$]. There was a significant difference on

the accuracy of the left caudate nucleus measure [F = 5.25, $p < .006$]. Further examination of this finding using Bonferroni corrections for alpha level found the significance between the NC group and the RD group to be $p < .014$ and between the NC group and the ADHD group to be $p < .016$. The left caudate nucleus accuracy rating was not used as a covariate in the following analyses due to the exploratory nature of this rating but will be used in the discussion.

Comparison of Brain Measurements for Groups

To address the first hypotheses, one-way analysis of variance (ANOVA) was used to investigate any significant differences on the brain measurements for the three groups (NC, RD, and ADHD). As described in the Methods chapter, measurements were made for each subject's right and left hemisphere. Brain measurements were made of the head of the caudate nucleus and area measurements were gathered for the caudate using the midline "best view" slice. Volummetric measurements were calculated using additional area measurements of the caudate, as described in the Methods chapter. Volume measures were not computed for one normal control and one ADHD subject due to the poor resolution of the MRI scan for these individuals.

Group descriptive statistics for the brain measurements are presented in Table 3. The groups did not differ on area measurements of the caudate for left [F = 1.11, $p < .337$] or right [F = 2.47, $p < .097$] or on volummetric measures for left caudate [F = .198, $p < .821$] or right caudate [F = .588, $p < .559$]. Bonferroni corrections failed to reveal any

Table 1

Means and Standard Deviations for Age, Full Scale IQ (FSIQ), Handedness, Gender, and Total Brain Area for Normal Controls, Reading Disabled (RD), and Attention-Deficit/Hyperactivity (ADHD) Groups

	Total Sample	Normal Controls	RD Group	ADHD Group
Age (in months)	117.44 (13.57) n=54	117.0 (14.97) n=12	117.0 (13.90) n=22	118.2 (13.02) n=20
FSIQ (WISC-III)	105.4 (15.93) n=52	113.42 (15.81) n=12	101.71 (15.39) n=21	104.37 (15.59) n=19
Handedness*	84.12 (27.25) n=51	79.5 (36.85) n=10	90.95 (12.71) n=21	79.25 (32.45) n=20
Gender (1=male,2=female)	1.33 (.48) n=54	1.58 (.51) n=12	1.27 (.46) n=22	1.25 (.44) n=20
Total Brain Area (cm^2)	173.02 (9.45) n=54	174.61 (10.15) n=12	174.14 (9.77) n=22	170.84 (8.69) n=20

* Edinburgh Handedness Inventory (positive values indicate right-handedness, negative values indicate left-handedness)

Table 2

Means and Standard Deviations for Accuracy and Quality Ratings on Caudate Nucleus (CN) Area Measurements for Normal Controls, Reading Disabled (RD), and Attention-Deficit/Hyperactivity (ADHD) Groups

Rating Type	Total Sample	Normal Controls	RD Group	ADHD Group
Accuracy* CN Area-Left	3.4 (.68)	2.8 (.58)	3.5 (.67)	3.5 (.61)
Accuracy CN Area-Right	3.1 (.94)	2.7 (.98)	3.4 (.85)	3.2 (.95)
Quality** CN Area - Left	3.2 (.63)	2.9 (.67)	3.4 (.58)	3.3 (.64)
Quality CN Area - Right	3.1 (.94)	2.7 (.98)	3.4 (.85)	3.2 (.95)

*Accuracy Rating of Measurement (5 point Likert scale): 1= poor accuracy, 2= minimal accuracy, 3= acceptable accuracy, 4= fair accuracy, 5= good accuracy
** Quality Rating of Scan (5 point Likert scale): 1= poor clarity, 2= minimal clarity, 3= acceptable clarity, 4= fair clarity, 5= good clarity

Table 3

Means and Standard Deviations for Brain Measurements for Normal Controls, Reading Disabled (RD), and Attention-Deficit/Hyperactivity (ADHD) Groups

Brain Region	Total Sample (n=54)	Normal Controls (n=12)	RD Group (n=22)	ADHD Group (n=20)
CN Area-Left (cm^2)	1.46 (.23)	1.37 (.26)	1.49 (.21)	1.48 (.22)
CN Area-Right (cm^2)	1.33 (.20)	1.24 (.23)	1.39 (.19)	1.32 (.18)
CN Volume-Left(cm^3)	13.40 (1.87)	13.14 (1.57)	13.37 (2.19)	13.59 (1.71)
CN Volume-Right(cm^3)	12.38 (1.54)	12.07 (1.21)	12.64 (1.74)	12.27 (1.48)

CN = Caudate nucleus

significant differences for the groups. Thus, the hypothesis that the groups would differ based upon size of the head of the caudate cannot be supported by these results.

Comparison of Hemispheric Asymmetry for Groups

In order to investigate the relationship between group identification and direction of asymmetry, a chi-square analysis of independence of these two variables was conducted. Proportion of group membership with R>L, L>R, or R=L asymmetry patterns are presented for caudate area (Table 4) and for caudate volume (Table 5). The results of the chi-square analyses revealed significant associations for asymmetry patterns for area [$\chi^2 = 26.33$, $p < .000$] and volume [$\chi^2 = 27.96$, $p < .000$]. These results support the hypothesis that groups would differ on asymmetry patterns. As examination of Tables 4 and 5 show, the ADHD group has a higher number of L>R asymmetry patterns compared to the normal control and RD groups for area measurements, but this difference diminishes when larger generalizations (i.e., volume measure) are considered. Comparisons of right and left hemisphere measurements were then conducted for each group to more closely evaluate these differences. A series of paired samples t-tests were conducted and these results are presented in Table 6. Within the normal control group, significant differences were found between the left and right caudate area [$\underline{t} = 2.96$, $p < .013$] and between the left and right caudate volume [$\underline{t} = 3.0$, $p < .003$]. Among the reading disabled group, significant differences were found between the left and right caudate area [$\underline{t} = 2.89$, $p < .009$] and also between the left and right caudate volume [$\underline{t} = 2.72$, $p < .013$]. The most robust findings were among the ADHD group, where

significant differences were noted for left and right caudate area [t = 5.36, $p < .000$] and between the left and right caudate volume [t = 5.66, $p < .000$].

Relationship between Caudate Size and Behavioral Variables

To examine the possibility of a relationship between caudate size and behavioral variables, Pearson correlations were obtained. A significance level of <.05 was used to screen for any significant relationships. Descriptive statistics for the behavioral variables (e.g., executive functioning and behavior ratings) on each group are presented in Table 7.

Correlations with Brain Measurements in ADHD Group

For the ADHD group, there were some significant relationships among the brain measurements. Correlations between the brain measurements were at the $p < .001$ level and correlations can be found in Table 8. Left caudate area was correlated with right caudate area (r = .78), left caudate volume (r = .95), and right caudate volume (r = .72). Right caudate area was correlated with left caudate volume (r = .71) and right caudate volume (r = .93). Left and right caudate volumes were associated with each other (r = .81).

Among the other groups, right and left caudate areas were correlated (r=.79), and left caudate volume was correlated with left and right caudate areas (r=.96 and r=.68, respectively). Right caudate volume was found to correlate with left and right caudate areas (r=.76, r=.97) and with left caudate volume (r=.78). All correlations for these measures were significant at the $p<.001$ level.

Table 4

Proportion of Group Membership Displaying Asymmetry for Caudate Nucleus Area Measurements

Group	R > L	L > R	R = L
Normal Controls	0%	25%	75%
Reading Disabled	4%	32%	64%
ADHD	0%	60%	40%

R = right hemisphere, L = left hemisphere

Table 5

Proportion of Group Membership Displaying Asymmetry for Caudate Nucleus Volume Measurements

Group	R > L	L > R	R = L
Normal Controls	0%	27%	73%
Reading Disabled	4%	32%	64%
ADHD	0%	47%	53%

Table 6

Comparison of Means for Caudate Nucleus Area and Volume

Group	Measurement	Comparison
Normal Control	CN Left Area v. CN Right Area CN Left Volume v. CN Right Volume	t = 2.96, $p < .013$ t = 3.0, $p < .013$
Reading Disabled	CN Left Area v. CN Right Area CN Left Volume v. CN Right Volume	t = 2.89, $p < .009$ t = 2.72, $p < .013$
ADHD	CN Left Area v. CN Right Area CN Left Volume v. CN Right Volume	t = 5.36, $p < .000$ t = 5.66, $p < .000$

CN = caudate nucleus

Correlations Between Brain Measures and Behavioral Variables

In the ADHD group, there were some correlations not evident among the other groups (NC + RD) between brain measures and behavioral variables. Left caudate volume was negatively correlated with RAS Color-Number-Letter Errors ($r = -.48$, $p < .05$) and BASC-PRS Attention Problems ($r = -.46$, $p < .05$). Right caudate volume was also associated with these two variables. Correlations with RAS Color-Number-Letter Errors ($r = -.63$, $p < .01$) and BASC-PRS Attention Problems ($r = -.59$, $p < .01$) were higher with the right caudate volume than with the left. For the ADHD group, the only executive functioning measure to have correlations with the behavioral data was WCST Number of Categories with SNAP-Teacher Rating of Impulsivity ($r = -.61$, $p < .01$).

In the other groups, there were significant findings between the measurement data and the behavioral variables. SNAP-Parent Rating of Impulsivity were found to correlate at the $p<.05$ level with left caudate area ($r=-.34$), right caudate area ($r=.39$), and right caudate volume ($r=.35$). SNAP-Teacher Rating of Impulsivity correlated with right caudate area ($r=-.38$) and right caudate volume ($r=-.36$) at the $p<.05$ level.

For both the ADHD and the other groups, there were numerous correlations between the behavior rating scales themselves and these can be found in Table 8. Note that the "other" groups include the normal controls and reading disabled subjects and exclude the ADHD subjects.

Table 7

Means and Standard Deviations for Psychometric Variables for Normal Controls, Reading Disabled (RD), and Attention-Deficit/Hyperactivity (ADHD) Groups

Test Variable	Total Sample	Normal Controls	RD Group	ADHD Group
BASC-PRS Attention Problems (t-scores)	66.3 (12.0) n=44	47.4 (9.2) n=9	69.4 (7.8) n=15	72.4 (5.5) n=20
BASC-PRS Externalizing Scale	60.5 (14.6) n=44	43.0 (8.7) n=9	61.3 (15.4) n=15	67.8 (8.7) n=20
BASC-PRS Hyperactivity Scale	62.5 (17.8) n=44	39.9 (7.8) n=9	63.0 (17.2) n=15	72.3 (11.5) n=20
BASC-TRS Attention Problems	61.4 (11.6) n=42	48.3 (11.5) n=8	62.8 (9.8) n=14	65.7 (9.1) n=20
BASC-TRS Externalizing Scale	55.7 (10.7) n=42	50.5 (11.6) n=8	58.4 (11.1) n=14	55.9 (9.8) n=20
BASC-TRS Hyperactivity Scale	59.3 (13.2) n=42	52.0 (14.9) n=8	62. 0 (12.3) n=14	60.3 (12.8) n=20
RAS Number of Errors (Raw scores)	.86 (.98) n=51	.55 (.82) n=11	.85 (.99) n=20	1.1 (1.1) n=20
Coding (WISC-III) (Scaled scores)	9.7 (3.3) n=52	12.9 (3.4) n=12	8.1 (2.6) n=21	9.3 (2.5) n=19
Categories (WCST) (Standard scores)	94.3 (20.8) n=47	108.3 (5.3) n=7	96.5 (18.6) n=20	87.3 (23.8) n=20
Failure to Maintain Set (WCST) (Standard scores)	93.0 (24.4) n=47	100.3 (24.7) n=7	91.0 (28.3) n=20	92.5 (20.6) n=20
SNAP-Parent Impulsivity Rating (Scaled scores)	8.36 (5.6) n=36	.00 (.00) n=3	7.85 (4.9) n=14	10.0 (5.3) n=19
SNAP- Teacher Impulsivity Rating	7.86 (5.1) n=34	4.0 (6.2) n=4	8.8 (4.9) n=13	8.1 (4.9) n=17

BASC-PRS (Behavior Assessment Scale for Children - Parent Rating Scale), BASC-TRS (BASC- Teacher Rating Scale), RAS (Rapid Alternating Stimulus - Color-Letter-Number Naming), WISC-III (Wechsler Intelligence Scale for Children, 3rd Edition), WCST (Wisconsin Card Sorting Test), SNAP (SNAP Checklist; Atkins, Pelham, & Licht, 1985)

Table 8

Correlations of Brain Measurements and Behavioral Variables for Other (Below Diagonal) and ADHD (Above Diagonal) Groups

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1 CN -L Area	--	.78*	.95*	.72*	-.07	-.18	-.25	.01	-.11	.17	.07	-.09	.09	-.20	-.29	-.11
2 CN-R Area	.79*	--	.71*	.93*	.04	-.35	.07	-.04	-.05	-.04	.05	-.00	-.03	-.14	-.37	-.18
3 CN-L Vol	.96*	.68*	--	.81*	-.14	-.48+	-.08	.17	-.17	.08	.16	.04	.22	-.01	-.46+	.06
4 CN-R Vol	.76*	.97*	.78*	--	-.08	-.63~	.27	.14	-.09	-.05	.18	.04	.09	.00	-.59~	-.03
5 Coding(WISC)	.30	.24	.33	.31	--	-.01	.38	.04	.29	-.32	.17	.25	.24	.02	-.01	-.08
6 RAS Errors	-.20	-.22	-.30	-.29	-.06	--	-.04	-.00	-.19	-.14	-.18	-.29	-.06	-.22	.15	-.39
7 WCST Cat	-.19	-.17	-.20	-.22	-.09	.36	--	.05	.05	-.61~	-.01	.02	-.25	-.05	-.30	-.26
8 WCST FTM	-.19	-.17	-.19	-.23	-.09	-.36	.99*	--	-.19	-.37	.15	-.25	.36	-.00	-.32	-.16
9 SNAP-P IM	-.34+	-.39+	-.29	-.35+	.18	.31	.52~	.51~	--	.59+	.54+	.71*	.40	.67~	.35	.02
10 SNAP-T IM	-.33	-.38+	-.28	-36+	.18	.31	-.36+	.36	.88*	--	.07	.66~	.03	.70~	.25	.28
11 BASC-P Ext	-.05	-.11	-.10	-.21	.27	.48~	.47~	.47~	.63*	.64*	--	.37	.69*	.25	-.11	-.04
12 BASC-T Ext	-.00	-.08	-.12	-.21	.24	.20	.23	.22	.61*	.74*	.74*	--	.23	.84*	.17	.26
13 BASC-P Hyp	-.05	-.10	-.10	-.21	.27	.48~	.47~	.47~	.63*	.64*	1.0*	.74*	--	.21	.05	-.17
14 BASC-T Hyp	-.00	-.08	-.12	-.21	.24	.20	.23	.22	.61*	.74*	.74*	1.0*	.74*	--	.29	.37
15 BASC-P Attn	-.05	-.11	-.11	-.22	.27	.48~	.47~	.47~	.64*	.64*	1.0*	.74*	1.0*	.74*	--	.39
16 BASC-T Attn	.00	-.08	-.12	-.21	.24	.20	.23	.22	.61*	.73*	.74*	1.0*	.74*	1.0*	.74*	--

+ $p < .05$, ~ $p < .01$, * $p < .001$ See next page for Table 8 notations

Table 8

Notations: CN-L (Caudate nucleus, left), CN-R (Caudate nucleus, right), Coding (Wechsler Intelligence Scale for Children, 3rd Edition), RAS Errors (Rapid Alternating Stimulus), WCST Cat (Wisconsin Card Sorting Test, Number of Categories), WCST FTM (WCST, Failure to Maintain Set), SNAP-P IM (SNAP Parent Rating, Impulsivity), SNAP-T IM (SNAP Teacher Rating, Impulsivity), BASC-P Ext (Behavior Rating Scale for Children- Parent Rating Scale, Externalizing Problems Composite), BASC-T Ext (BASC-Teacher Rating Scale, Externalizing Problems Composite), BASC-P Hyp (BASC Parent Rating, Hyperactivity Scale), BASC-T Hyp (BASC-Teacher Rating, Hyperactivity Scale), BASC-P Attn (BASC Parent Rating, Attention Problems Scale), BASC-T Attn (BASC-Teacher Rating, Attention Problems Scale)

CHAPTER V

DISCUSSION

The primary objective of this research study was to explore potential differences in brain morphology in children with ADHD. Specifically, it was hypothesized that children with ADHD would demonstrate a significant difference in the size of the head of the caudate nucleus, a brain region implicated in behavioral disinhibition. A second objective for the study was to investigate whether any structural differences, if found, were correlated with behavioral variables. These included performance-based tasks on measures emphasizing executive functioning and ratings of behavior that may be associated with disinhibition. In this chapter, the main findings of the study are discussed along with any limitations in the current study and implications for future research. The main hypotheses of this study are restated below:

1. Children with ADHD do not differ from normal controls and a clinical group in the size (area, volume) of the head of the caudate nucleus.
2. The children with ADHD do not display a different pattern of asymmetry in the caudate nucleus when compared to the other groups.
3. The variations in caudate morphology are not related to performance on measures of behavioral inhibition and executive functioning for the total sample or the ADHD group.

4. The magnitude of the measurements for the caudate nucleus will not display any relationship to the direction of any existing correlations. Specifically, higher ratings of behaviors of disinhibition and motor over-activity (e.g., hyperactivity, impulsivity, externalizing behaviors) will not be associated with smaller caudate size. Lower ratings of performance on executive functioning will not be correlated with smaller caudate size.

In regards to Hypothesis 1, that differences in caudate size could be detected in children with ADHD compared to other groups, the results failed to reject this hypothesis. The only finding that approached significance was for right caudate area to differ between groups [$F = 2.27$, $p < .097$]. An examination of group means for area and volume indicates a trend for right caudate measurements to be smaller than left caudate for all groups. Mataro, et al., (1997) who also examined the head of the caudate nucleus, found that the adolescents with ADHD had significantly smaller right caudate areas than control subjects. Similar to findings by Castellanos, et al., (1994), caudate area measurements for this sample correlated highly with the volume measurements. In their study, a developmental trend was found across the adolescents where greater size differences were assessed in the older subjects. The authors attributed their finding to synaptic pruning. When these findings are related to this study, it may by proposed that in younger (pre-adolescent) subjects there is less evidence for morphological differences between groups because there has been less opportunity for the natural process of synaptic pruning. These findings lend support for the hypothesis that structural differences may not exist from birth, but rather develop over time as the result of faulty

growth mechanisms (e.g., lack of synaptic pruning or overpruning). Because synaptic pruning is a process that contributes to efficiency in processing, perhaps children with ADHD are less effective at inhibitory processes because their system is less efficient.

When the findings regarding Hypothesis 2, that differences in patterns of asymmetry could be determined between groups, the data produced interesting results. Hypothesis 2 can be rejected because significant differences were found between groups for caudate asymmetry patterns. To aid in the discussion of these results, a comparison of these results with other research is reported in Table 9. When patterns of asymmetry are examined, the majority of studies have found a R < L asymmetry pattern among normal controls (Hynd, et al., 1993; Filipek, et al., 1997; Mataro, et al., 1997), while one study (Castellanos, et al., 1994) found R > L pattern in their sample. This author found a trend for R = L, or lack of asymmetry, for area and volume among normal controls. One hypothesis is that this may be the result of a younger sample than some of the other research, although Hynd's study was of a similar age range and did find asymmetry. When the ADHD group trends are inspected in the literature, a R > L or R = L pattern is evident (see Table 9). In this study, a R = L pattern was found for volume, although a L > R trend was noted for area. It may have been that the sample size was too small to pick up statistically sigificant asymmetry with the area measurement.

However, within each group, significant differences between size were found between the right and left caudate. Significant differences in size were found between the left and right caudate in the normal control group for area and volume. When looking at

Table 9

Asymmetry Patterns Across Research Findings for ADHD and Normal Controls*

Research Study	ADHD Group	Normal Control Group
Current Study (ages 8-12)	R < L (area) R = L (volume)	R = L (area) R = L (volume)
Hynd, et al., (1993) (ages 8-12)	R > L (area)	R < L (area)
Castellanos, et al., (1994) (ages 6-19)	R = L (volume)	R > L (volume)
Filipek, et al., (1997) (ages 9-17)	R = L (volume)	R < L (volume)
Mataro, et al., (1997) (age 14)	R > L (area)	R < L (area)

* For the purposes of summarizing findings, studies examining the caudate nucleus are not identical in (1) orientation of slice, e.g., axial v. coronal, (2) type of measure, e.g., area v. volume, and (3) region of measurement, e.g., head of caudate v. head and body of caudate

group means, a L > R trend was found for each measurement. When results for the ADHD group were examined, significant differences between left and right caudate were found for area and volume. An examination of measurement means reveals that there was also a L > R trend observed. This helps explain why no group differences were found between groups, but does not clear up the inconsistent findings that exist in the literature on asymmetry.

Hypothesis 3, that a relationship between structural size and behavioral data exists, cannot be rejected at the $p < .01$ level for the other groups. If a less stringent alpha level is used ($p < .05$), then some relationships do emerge (see Table 10). For the other groups, relationships between the measurement data and the behavioral data can be found. As left caudate area increases, performance on one of the executive functioning measures (WCST Number of Categories) decreases, or becomes worse. This would support the idea that less pruning (as may be indicated by larger size) may correlate with decreased efficiency in problem-solving. Additionally, as left caudate volume and right caudate volume increase, the number of RAS errors is decreased. At first glance this may appear to be a contradictory finding when considering that larger caudate area was related to poorer performance on the WCST. However, the two tasks, although both related to frontal lobe functioning do measure different types of skills. The WCST requires problem-solving in a novel situation and the ability to respond to external feedback of performance. The RAS requires inhibition of responding, speed of processing, and the ability to respond to internal feedback. It may be that the caudate plays a different role in the execution of these two kinds of skills.

There was some relationship between the executive functioning variables and the behavioral data which suggested that problems with executive functioning may be associated with greater behavioral problems. For example, better performance on WISC-III Coding was related to fewer RAS errors and ratings of attention problems (BASC-PRS, BASC-TRS). Additionally, better performance on the WCST (Number of Categories) was associated with lower ratings of impulsivity (Teacher SNAP), externalizing problems (BASC-PRS), hyperactivity (BASC-PRS), and attention problems (BASC-PRS, BASC-TRS). The fact that WISC-III Coding was correlated with the RAS but not with the WCST supports the idea that they are measuring two discrete skills.

When the ADHD group is examined, some similar findings emerge. Within the ADHD group, when left and right caudate volume increases, the number of RAS errors decreases. Additionally, when left and right caudate volume increases, the Attention Problems decreases (BASC-PRS). The only other relationship of interest to this discussion is that for the ADHD group, poorer performance on the WCST (Number of Categories) was associated with higher ratings of impulsivity (SNAP-T), as was found for the other groups.

These trends contradict Hypothesis 4, that greater problems with inhibition are associated with smaller caudate size. In fact, it is larger size that is more detrimental to performance or behavior problems. In the only other study that has looked at behavioral variables in relation to caudate size, Mataro, et al., (1997) found that in their total sample of adolescents larger right caudate area was associated with worse performance on attentional tasks (PASAT, Brown-Peterson distractor paradigm), immediate visual recall

Table 10

Trends for Correlations Between Measurement and Executive Functioning Variables for the Other and Attention-Deficit/Hyperactivity (ADHD) Groups

Correlation	Other Groups	ADHD Group
Size	as CN-L area ⇑, WCST Cat	as CN-L vol ⇑, RAS err
	as CN-L vol ⇑, RAS err	as CN-R vol ⇑, RAS err
	as CN-R vol ⇑, RAS err	as CN-L vol ⇑, BASC-P Att
		as CN-R vol ⇑, BASC-P Att
Exec. Functioning	as Coding ⇑, RAS err	as WCST Cat , SNAP-T Im
	as Coding ⇑, BASC-P Att Prob	
	as Coding ⇑, BASC-T Att Prob	
	as WCST Cat ⇑, SNAP-T Im	
	as WCST Cat ⇑, BASC-P Ext	
	as WCST Cat ⇑, BASC-P Hyp	
	as WCST Cat ⇑, BASC-P Att	
	as WCST Cat ⇑, BASC-T Att	

CN-L = caudate nucleus left, CN-R = caudate nucleus right, vol = volume, =decreases, ⇑ = increases, WCST Cat = Wisconsin Card Sorting Test, Number of Categories, RAS err = RAS Number of Errors, Coding = WISC-III Coding, SNAP-T Im = SNAP-Teacher Impulsivity Rating, BASC-P Att Prob = BASC-Parent Rating Scale, Attention Problems, BASC-T Att Prob = BASC-Teacher Rating Scale, Attention Problems, BASC-P Hyp = BASC-Parent Rating Scale, Hyperactivity, BASC-P Ext = BASC-Parent Rating Scale, Externalizing Problems Composite

(Rey-Osterrieth complex figure), and higher ratings on the Conner Teachers Rating Scale (CTRS). Larger left caudate area was associated with poorer performance on an attentional task (Brown-Peterson), verbal list learning (Auditory Verbal Learning Test), and higher ratings on the CTRS. The current study can make similar claims in that larger caudate volumes were associated with worse performance on some of the behavioral ratings and on the WCST. However, because larger left and right caudate volumes were related to RAS errors, it is difficult to make a general statement addressing the influence of laterality. This difficulty may reflect differences in task demands among the various test measures.

When some of the previous metabolic research is reviewed, lower metabolic rates of methylphenidate (Ritalin) has been found to occur in the right striatum (Lou et al., 1984; Lou, et al., 1989). When Table 9 is re-examined, it can be determined that generally, a lack of asymmetry or reversed asymmety (R > L) is evident in subjects with ADHD. Perhaps a dysfunction in the degree of synaptic pruning or some other neurodevelopmental process exists in individuals with ADHD. There is not a consensus among existing studies for age of study, and this fact may help explain why contradictory findings or a failure to find significant differences can be seen in the literature. If structural variations are occurring at some time along an individual's course of development, it would be important to look at trends across age groups, as was done by Castellanos, et al., (1994). It may be that larger size rather than smaller size reflects more abnormality among this population, contrary to the original statement made in Hypothesis 4.

Limitations of Study

A number of limitations for this study involves the methodological difficulties that exist with imaging research. The technology in imaging research has advanced so that stronger and more powerful scanners are now being utilized than was originally available for this study. More powerful scanners would produce MRI scans with greater resolution and less artifact. Another limitation of this study is the fact that movement artifacts limited the quality of the measurements. As the qualitative analysis indicated, confidence in accuracy was significantly different for right and left caudate area measurements. Therefore, it may have been helpful to use accuracy ratings as a covariate in the analyses. This was not done because of the qualitative nature of this type of measure, but it may have provided some interesting findings. It could be argued that accuracy of measurement influenced the group findings for size differences. Perhaps a significant difference in caudate size would have emerged between groups if accuracy had been taken into account. As a review of the literature indicates, qualitative ratings of measurement have not been used when interpreting data. Perhaps this will become a standard in measurement research that will help generate consistency in findings.

Another limitation of this study is that other studies in the literature have examined various regions of the caudate. Other areas, such as the body and tail of the caudate nucleus have been included. This makes comparison across different research more difficult. The development of a standardized brain measure would assist in greater continuity among studies. The problem can be seen by considering the variability in the

types of orientations that are used among existing research (e.g., horizontal plane, coronal plane) and in the types of measurement collected (e.g., area, volume). The importance of standardizing methodology across future research studies is important to aid in replication studies.

A limitation of this study, which is common among imaging research, is the small sample size. Additionally, the unequal group sizes affects the types of analysis that can be done and the confidence with which it can be interpreted. The small groups sizes may have also have an effect on the confidence in the correlational findings, due the the number of correlations conducted. Ideally, larger groups with equal numbers of subjects would have allowed for more in-depth analysis. For example, if the number of subjects were expanded, multiple regression could have been utilized to examine the data. A related limitation is the fact that gender and handedness were not used as variables for analysis. Given the relationship that these two characteristics may have with hemispheric differences, these may be important to examine. Perhaps more striking findings would emerged if there had been a more equal distribution within groups for gender (most subjects were male) and handedness (most subjects were right handed). The ratio of male/female and left/right handedness may have differed in other studies that found significant differences between groups. Another methodological limitation of the study involves the fact that the ADHD subtypes were included in the analyses. Future studies would improve upon this one if a larger sample of each ADHD subtype was gathered so that differences between subtypes could be investigated.

Lastly, an examination of outliers in each group would have improved upon the analyses. Outliers on the behavioral measures may have influenced the overall group findings, and contributed to the final results. For example, outliers within the normal control or reading disabled groups may have reduced the chance of detecting a signficant difference between one of those groups and the ADHD group. Additionally, an examination of outliers on the behavioral ratings and neuropsychological test data may have helped clarify measurement findings. It may have been that greater pathology, as indicated by higher ratings of behavior problems or lower test performance, was correlated with either larger or smaller caudate measurements.

Implications for Future Research

Although this study failed to find support for the hypothesis that children with ADHD would differ from other groups in the size of the head of the caudate nucleus, there are still implications for future research in this area. First, imaging studies on clinical groups remains an expanding area of research that is fraught with inconsistencies in methodology and techniques. One can hope, however, that the culmination of many studies will begin to shed light on a common finding that can be seen as a reliable. This study adds to the existing data and provides another data point to the available research. Eventually, a meta-analysis may lead to more concrete findings that can be used to understand the underlying mechanisms of ADHD.

Second, the review of the literature undertaken in this study lends support for functional studies between structure and function. If the role of the caudate nucleus is seen in the management of a frontal-striatal system, then perhaps the key to understanding

the impact of neurodevelopmental differences is best studied through techniques that examine how that system may function differently in children with ADHD. Functional MRI research, which continues to show promise in the field of neuroimaging may led to greater exploration in the study of ADHD. This may also be the most promising avenue for studying how lateralization and brain developmental patterns may have an impact on the presentation of this disorder. New research examining the effects of stimulant medication on children's performances on a neuropsychological task involving lateralization implicate a lateralized dysfunction in frontostriatal systems (Sheppard, Bradshaw, Mattingley, and Lee, 1999). Creating a functional imaging study involving a similar methodolgy may add to the support for asymmetry patterns in ADHD.

New theoretical models continue to support the role of the caudate nucleus as an integral component of a frontal-striatal circuit that serves to provide positive and negative feedback to other cortical regions. For example, Castellanos (1997) discussed the role that dopamine plays in this circuit through inhibition of certain receptors located in the frontal cortex and the striatum. Barkley's (1997) model suggests that the inhibition seen in ADHD can be linked to four executive functions: working memory, self-regulation, internalization of speech, and reconstitution (synthesis). These models need to be explored with empirical work and neuroimaging studies. It would be interesting to expand this study to involve looking at brain measurements in relation to performance on tasks in each of these executive functions.

Finally, this study supports the idea that certain "mental" disorders, as ADHD is classified, result from variations in normal neurodevelopment. What mechanisms may

play a role in altering the course of normal growth? Will genetic or environmental factors, or a combination of the two, be identified as having the most impact? If developmental processes like pruning are implicated, can they be influenced or altered by treatment? As more research leads to greater understanding, the hope is that new ways to treat and/or prevent ADHD can be identified. Additionally, as knowledge about one area of brain development and functioning grows, more gains are made in regards to other brain mechanisms and disorders.

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