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MOTOR PATTERNS IN ATTENTION DEFICIT HYPERACTIVITY DISORDER

by

DARRELL JAMES PANICH

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of

MASTER OF SCIENCE

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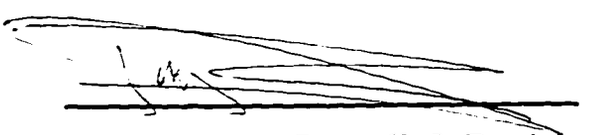

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The undersigned certify that they have read and recommended to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled MOTOR PATTERNS IN ATTENTION DEFICIT HYPERACTIVITY DISORDER submitted by DARRELL JAMES PANICH in partial fulfillment of the requirements for the degree of MASTER OF SCIENCE.

Roger C. Bland

Thomas J. Snyder

Andrew J. Greenshaw

Arthur Prochazka

October 1, 1997

Prevent trouble before it arises.
Put things in order before they exist.
The giant pine tree grows from a tiny sprout.
The journey of a thousand miles starts from beneath your feet.

Rushing into action, you fail.
Trying to grasp things, you lose them.
Forcing a project to completion, you ruin what was almost ripe.

-Lao-Tzu
Tao Te Ching

Abstract

The motor patterns of children with attention-deficit hyperactivity disorder (ADHD) were studied. Two groups, each of 24 male subjects (average age 9.79 years), were tested off medication(s). Subjects completed four motor tests (grooved pegboard, finger tapping, Purdue pegboard, and hand dynamometer) and were compared on measures of preferred and non-preferred hand performance, performance asymmetry, and prevalence and consistency of asymmetry. ADHD subjects demonstrated significantly poorer performance with their preferred hand on the Purdue pegboard test as compared to normal control subjects. Fewer ADHD subjects showed deviation from symmetrical performance than did normal controls for the grooved pegboard test. No differences in performance, asymmetry, prevalence, or consistency of asymmetry were found on any of the remaining motor tests. These results suggest that ADHD children differ in performance of manual dexterity tasks compared to non-ADHD subjects. The relation of motor system function to hyperactivity in ADHD children is discussed.

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List of Abbreviations and Symbols

ADHD	attention deficit hyperactivity disorder
ANCOVA	analysis of covariance
ANOVA	analysis of variance
CT	computed axial tomography
CBCL	Child Behavior Checklist
CBF	cerebral blood flow
CMR_{glu}	cerebral glucose metabolism
CPRS-R	Conners' Parent Rating Scale-Revised
DR	dominance ratio
DSM-IV	*Diagnostic and Statistical Manual of Mental Disorders-4th Edition*
DYN	hand dynamometer
FTT	finger tapping test
GPT	grooved pegboard test
LQ	laterality quotient
MANCOVA	multivariate analysis of covariance
MRI	magnetic resonance imaging
NP	non-preferred hand
PET	positron emission tomography
PPB	Purdue pegboard

Pr	preferred hand
SPECT	single-photon emission computed tomography
α	alpha (significance level)
χ^2	chi-square (statistic)
>	greater than

A Introduction

Attention deficit hyperactivity disorder (ADHD) is one of the most common childhood developmental disorders that accounts for about 50% of child psychiatry clinic populations (Cantwell, 1996). Prevalence in the general population is around 3-7% of school-age children (Cantwell, 1996; Barkley, 1997). Males are over-represented in this disorder by 3:1 (Barkley, 1997) or as much as 9:1 in clinically referred samples (Cantwell, 1996). ADHD is not just a childhood disorder, studies have found that ADHD persists into adolescence in 50-80% of all cases and into adulthood in 30-50% of all cases (Barkley, 1997).

This common disorder can dramatically affect children and their families through financial cost, stress to families, disruption in schools, and the potential for other problems later in life. ADHD subjects are at greater risk in relation to a variety of factors, including: low academic achievement, poor school performance, grade retention, increased school suspensions or expulsions, poor peer and family relations, anxiety and depression, conduct problems, delinquency, early substance abuse, increased driving accidents and infractions, and difficulties in adult relationships, marriage, and employment (Barkley, 1990, 1997). All of these risks can be exacerbated by

comorbid disorders that are commonly found with ADHD (e.g.: Tourette syndrome, conduct disorder, learning disorder) (Barkley, 1990, 1997; Yeates and Bornstein, 1994).

As the name implies and as defined by the *Diagnostic and Statistical Manual of Mental Disorders - 4th Edition* (DSM-IV), ADHD consists of two major symptoms: inattention and hyperactivity-impulsivity (Table 1) (American Psychiatric Association, 1994). The inattention component of ADHD is expressed through symptoms of not listening, difficulty in organizing tasks, and making careless mistakes in work or other activities (see Table 1). Symptoms of hyperactivity-impulsivity include being fidgety, talking excessively, and intruding on others (see Table 1). To attain a diagnosis of ADHD, a person must exhibit these symptoms for at least six months in two or more settings (e.g., at school, home, etc.). These symptoms also must be evident before the age of seven years to a degree that caused significant behavioral impairment (see Table 1). There are three major subtypes of ADHD: the predominantly inattentive type, the predominantly hyperactive-impulsive type, and the combined type, showing symptoms of both inattention and hyperactivity-impulsivity.

Table 1: *DSM-IV Diagnostic Criteria for Attention Deficit Hyperactivity Disorder*

A Either (1) or (2):

A.1 six (or more) of the following symptoms of **inattention** have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

Inattention

A.1.1 often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities

A.1.2 often has difficulty in sustaining attention in tasks or play activities

A.1.3 often does not seem to listen when spoken to directly

A.1.4 often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behaviour or failure to understand instructions)

A.1.5 often has difficulty in organizing tasks and activities

A.1.6 often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)

A.1.7 often loses things necessary for tasks and activities (e.g., toys, school assignments, pencils, books, or tools)

A.1.8 is often easily distracted by extraneous stimuli

A.1.9 is often forgetful in daily activities

A.2 six (or more) of the following symptoms of **hyperactivity-impulsivity** have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

Hyperactivity

A.2.1 often fidgets hands or feet or squirms in seat

A.2.2 often leaves seat in classroom or in other situations in which remaining seated is expected

A.2.3 often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)

A.2.4 often has difficulty in playing or engaging in leisure activities quietly

A.2.5 is often "on the go" or often acts as if "driven by a motor"

A.2.6 often talks excessively

Impulsivity

A.2.7 often blurts out answers before questions have been completed

A.2.8 often has difficulty awaiting turn

A.2.9 often interrupts or intrudes on others (e.g., butts into conversations or games)

B Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age 7 years.

C Some impairment from the symptoms is present in two or more settings (e.g., at school [or work] and at home).

D There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning.

E The symptoms do not occur exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder and are not better accounted for by another mental disorder(e.g., Mood Disorder, Anxiety Disorder, Dissociative Disorder, or a Personality Disorder).

Code based on type:

314.01 Attention Deficit/Hyperactivity Disorder, Combined Type : if both Criteria A1 and A2 met for the past 6 months

314.00 Attention Deficit/Hyperactivity Disorder, Predominantly Inattentive Type: if Criterion A1 is met but Criterion A2 is not met for the past 6 months

314.01 Attention Deficit/Hyperactivity Disorder, Predominantly Hyperactive-Impulsive Type: if Criterion A2 is met but Criterion A1 is not met for the past 6 months

Coding note: For individuals (especially adolescents and adults) who currently have symptoms that no longer meet full criteria, "In Partial Remission" should be specified.

[Based on information from the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition.* Copyright 1994 American Psychiatric Association.]

The precise cause of ADHD has yet to be determined, although there is evidence for a biological basis. Neuroimaging studies of ADHD patients point to abnormalities in the frontal lobe (Castellanos et al., 1994, 1996; Hynd et al., 1990; Lou et al., 1984; Amen et al., 1993; Zametkin et al., 1990, 1993; Ernst et al., 1994b), basal ganglia (Lou et al., 1984, 1989, 1990; Castellanos et al., 1994, 1996; Aylward et al., 1996; Singer et al., 1993; Hynd et al., 1990) and other neural structures (Hynd et al., 1990, 1991, 1993; Zametkin et al., 1993; Ernst et al., 1994b; Lou et al., 1984, 1989, 1990; Castellanos et al., 1994, 1996; Semrud-Clikeman et al., 1994; Geidd et al., 1994; Baumgartner et al., 1996; Lyoo et al., 1996). Other researchers have found that there is a familial component to ADHD, indicating that there is heritable transmission of the disorder (Biederman et al., 1992; Cantwell, 1996). Since ADHD is managed pharmacologically by drugs like methylphenidate (Ritalin®), there have been suggestions that there is a low turnover of neurotransmitters in the brain of ADHD patients (Zametkin and Rapoport, 1987; Cantwell, 1996).

There is no quick, one test method to diagnose ADHD. Rather, clinicians diagnose ADHD by looking at the overall history of patient behavior. Various behavior rating scales filled out by parents and teachers, along with clinical interview and observation of the patient,

provide the clinician with the necessary information to diagnose ADHD (Barkley, 1990 for review).

In neuropsychological testing, the performance of ADHD subjects has been found to be similar to patients with frontal lobe damage (Shue and Douglas, 1992; Benson, 1991; Heilman et al., 1991). Difficulty in regulating cognitive processes, attention, memory, and learning deficits (Arcia and Gualtieri, 1994; Seidman et al., 1995), and problems in language, motor and frontal executive functions (Seidman et al., 1995, 1997a, 1997b; Carte et al., 1996) have been reported in neuropsychological testing with ADHD subjects. ADHD subjects actually perform at a level almost two years behind age-matched cohorts on some neuropsychological tests (Shue and Douglas, 1992). As the frontal lobes, basal ganglia, and other structures that influence motor control show deviance from normality in ADHD subjects, and that hyperactivity, defined as excessive *motor* behavior, is a component of ADHD, the present study was performed to further explore the extent of motor disruption in ADHD.

In the following sections a review of motor systems will be presented which will be followed by a review of neuroimaging findings in ADHD.

Finally, neuropsychological testing procedures on ADHD subjects will be summarized with a focus on the motor system.

A.1 The Motor System

There are three major brain regions that make up the motor system in humans. The frontal lobe performs many functions in humans including motor control (Luria, 1973; Brooks, 1986; Benson, 1991; Heilman et al., 1991; Ghez, 1991a; Shue and Douglas, 1992; Barkley et al., 1992). Four areas of the frontal lobe; the primary motor cortex, premotor cortex, supplementary motor area and the prefrontal cortex, play a specific role in motor control (Figure 1). The cerebellum, located at the caudal aspect of the brain (Figure 1), is another area that has a major influence on motor control (Ghez, 1991b, Kawato, 1995, Houk and Wise, 1995, Horne and Butler, 1995). Another region involved in motor control is a group of nuclei called the basal ganglia (Figure 2). The five components of the basal ganglia are the caudate nucleus and putamen (together known as the striatum), globus pallidus (internal and external segments), substantia nigra (pars compacta and pars reticulata), and the subthalamic nucleus. The basal ganglia are involved in many functions including motor control (Reviews of basal gangila function can be found in: Divac and Öberg, 1979; McGeer and McGeer, 1987; Albin et al., 1989; Alexander and

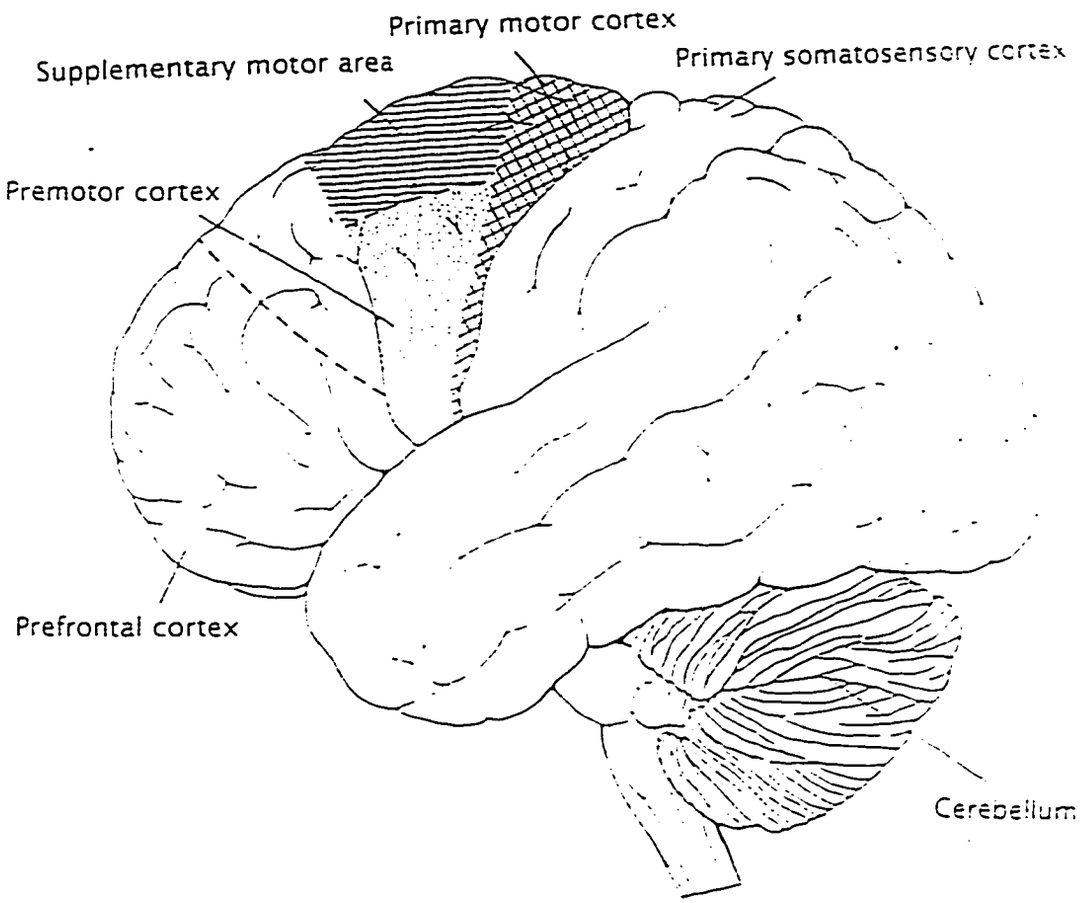


Figure 1. A lateral view of the human brain showing the location of the cerebellum and frontal cortical motor areas (adapted from Ghez, 1991a).

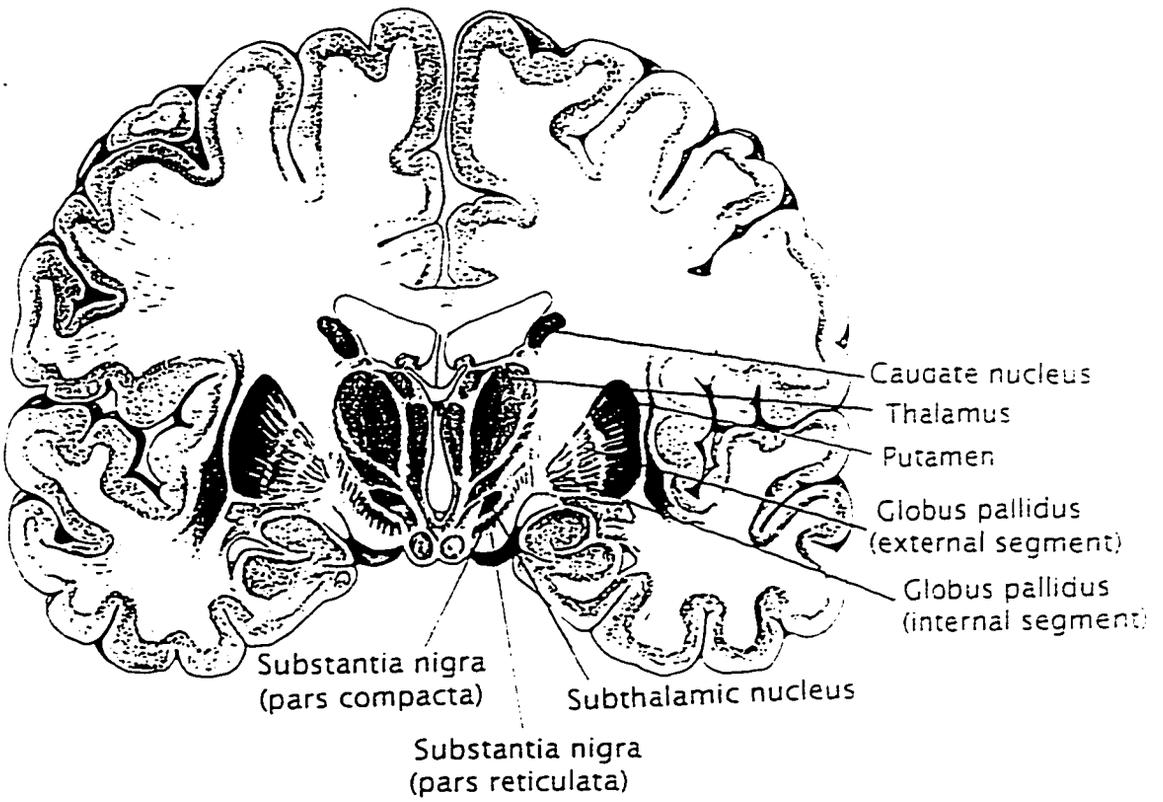


Figure 2. A coronal section of the human brain showing the location of the thalamus and nuclei that compose the basal ganglia (adapted from Côté and Crutcher, 1991).

Crutcher, 1990; Côté and Crutcher, 1991; Jaeger et al., 1993; Alexander, 1995; Chesslet and Delfs, 1996). The interconnections of the basal ganglia nuclei form a 'motor circuit' that processes information for motor control. As each of the three motor areas plays a unique role in the control of motor behavior, dysfunction in any one area will show particular irregularities in motor patterns (Albin et al., 1989, Alexander and Crutcher, 1990, Ghez, 1991a, 1991b, 1991c, Chesslet and Delfs, 1996).

A.1.1 The Frontal Lobe

As stated earlier, the areas concerned with motor control in the frontal lobe are the primary motor cortex, premotor cortex, supplementary motor area and the prefrontal cortex (also known as the motor association area) (see Figure 1). These cortical areas are interconnected within the same hemisphere and between hemispheres. The primary motor cortex, premotor cortex, and supplementary motor area provide the major output from the frontal motor systems to the brainstem, basal ganglia, cerebellum, and to the muscles (via the spinal cord). Input to the frontal motor areas arrives from three major sources: the periphery, basal ganglia, and cerebellum(Ghez, 1991a). These afferents project to the primary motor cortex via the thalamus or via the premotor areas (premotor cortex

and supplementary motor area). Also, the primary motor cortex receives homotopic (same parts of body map are interconnected) afferents from the somatosensory and sensory association areas.

Each of the frontal motor areas subserves a different function in motor control. The primary motor cortex is responsible for the initiation and control of movements. The strength of force, rate of change of force and direction of force are encoded by the primary motor cortex (Ghez, 1991a). It has been noted that the cells of the primary motor cortex fire more in association with willed movements than to more automatic or reflexive types of movement, including emotional responses (Ghez, 1991a). Lesions of the premotor areas (premotor cortex and supplementary motor area) impair the ability to develop appropriate movement strategies (Ghez, 1991a). These areas are more concerned with the programming of complex movements and coordination of posture and balance in response to voluntary movement. The premotor cortex also contains 'set-related' neurons that fire when preparing to make a movement.

A.1.2 The Cerebellum

The role of the cerebellum in motor control is that of a comparator which compares the motor plan or intention with motor performance.

In making the comparison between intention and performance, the cerebellum is able to correct and scale ongoing movements to ensure that subsequent movements fulfill the intention or goal (Ghez, 1991b).

The cerebellum itself is composed of three lobes, the anterior, posterior, and flocculonodular lobes (Figure 3). Afferent and efferent information travels through the cerebral peduncles located at the base of the cerebellum. Two longitudinal furrows are evident when viewing the cerebellum directly from the back of the brain. The vermis is the longitudinal protuberance located on the midline of the cerebellum. On either side of the vermis are the cerebellar hemispheres composed of two parts, an intermediate and lateral zone.

There are three main functions of the cerebellum. The first is maintaining balance (equilibrium) and in coordinating eye and head movements (Ghez, 1991b). This function is controlled by the flocculonodular lobe that receives afferent connections from the vestibular labyrinth and sends efferent connections to the vestibular nuclei in the brainstem. The next function of the cerebellum is to take part in the execution of movement and regulation of muscle tone (Ghez, 1991b). The vermis, which affects axial and proximal movement execution, receives information from proximal body parts

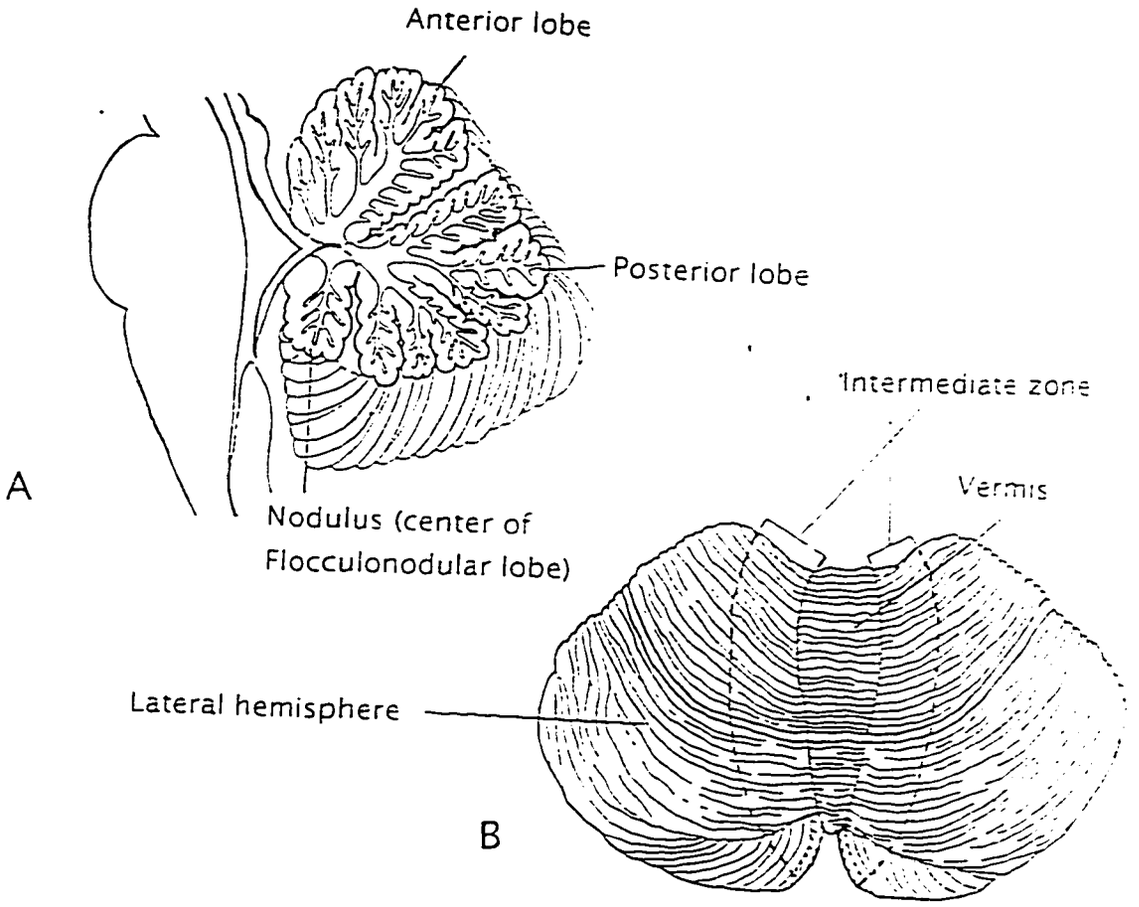


Figure 3. The cerebellum. (A) a sagittal section of the cerebellum showing the three lobes. (B) a superior view of the cerebellum showing the three cerebellar divisions. (adapted from Diamond et al., 1985).

and projects out to axial and proximal systems in the motor cortex. The intermediate zones of the lateral cerebellar hemispheres, that receive spinal afferents from distal body parts, project to lateral systems of the brainstem and motor cortex to control distal body parts during ongoing movement. The final function of the cerebellum is the initiation, planning, and timing of movements (Ghez, 1991b). Functions like spatial coordination, initiation and termination of movement, scaling the amplitude and temporal coordination of movement are handled by the lateral zones of the cerebellum. The lateral hemispheres of the cerebellum receive input from the somatosensory and motor cortices and project to the premotor and motor cortices

A.1.3 The Basal Ganglia

The basal ganglia are composed of five subcortical nuclei: the caudate nucleus and putamen (together known as the striatum), globus pallidus (internal and external segments), substantia nigra (pars compacta and pars reticulata), and the subthalamic nucleus. These nuclei are interconnected with each other to form a motor circuit (Figure 4) (Alexander and Crutcher, 1990; Alexander, 1995). Most cortical input to the basal ganglia enters through the striatum (primarily the putamen). From the striatum there are two pathways

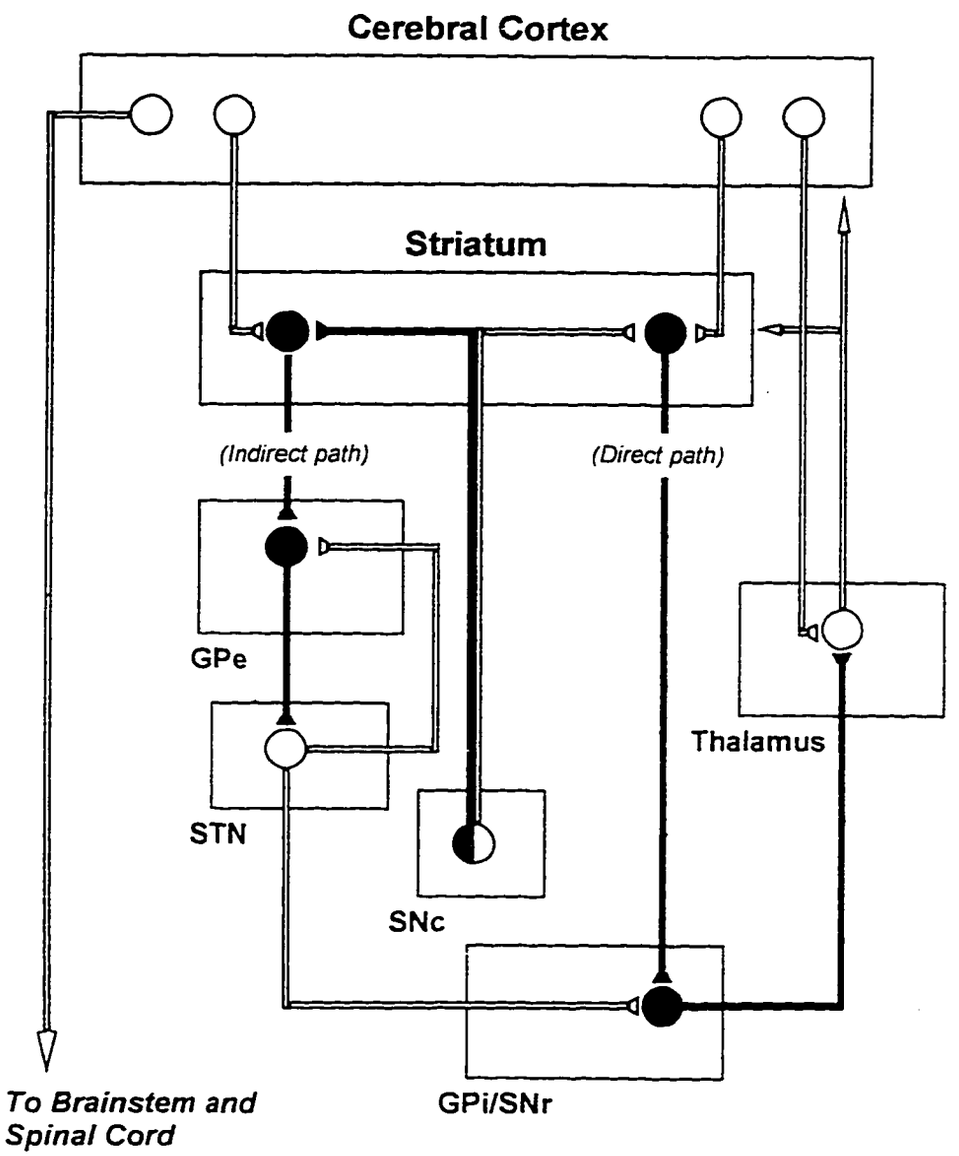


Figure 4: A schematic of the basal ganglia motor circut including connections with the thalamus and cerebral cortex. Inhibitory neurons are shown as filled in. Abbreviations are as follows: GPe- external segmant of globus pallidus, STN- subthalamic nucleus. SNc- substantia nigra pars compacta, GPi- internal segment of the globus pallidus, SNr- substantia nigra pars reticulata. (adapted from Alexander and Crutcher, 1990)

that carry information to the output nuclei of the basal ganglia (internal globus pallidus and substantia nigra pars reticulata). The direct pathway is an inhibitory path from the striatum to the internal globus pallidus and substantia nigra pars reticulata complex. The indirect pathway has an inhibitory projection from the striatum to the external globus pallidus. From the external globus pallidus a further inhibitory connection is made to the subthalamic nucleus. From the subthalamic nucleus, an excitatory synapse is made with the output nuclei of the basal ganglia. The subthalamic nucleus, which also receives excitatory cortical input, also sends a collateral projection back to the external globus pallidus to complete a negative feedback loop. From the internal globus pallidus and substantia nigra pars reticulata output nuclei, an inhibitory connection is made out of the basal ganglia to the thalamus that, in turn, sends excitatory projections back to the supplementary motor area, premotor cortex, primary motor cortex, and prefrontal cortex. The substantia nigra pars compacta influences the basal ganglia motor circuit through mixed projections to the striatum. These projections are mixed in that the substantia nigra pars compacta has different influences on the direct (excite) and indirect (inhibit) pathways in the basal ganglia motor circuit.

The functions of the basal ganglia are not as clearly defined as those of the cerebellum. However, it is known that the basal ganglia are involved in the higher-order cognitive aspects of motor control. In this role the basal ganglia are involved in the planning and execution of complex movement strategies related to discrete and directionally selective single-joint movements of the body (Alexander and Crutcher, 1990; Alexander, 1995). The basal ganglia are not involved in the initiation of stimulus triggered movements or amount of muscle force required to complete a movement (Alexander and Crutcher, 1990; Alexander, 1995). Rather they are involved in things like the preparation of target selection and what Jager et al. (1993) have called 'motor readiness' (preparing for the timing of the onset of movement). Also, Mink and Thach (1993) have hypothesized that the basal ganglia are important in inhibiting certain postural and antagonistic muscles to allow movement to proceed without opposition. There is evidence for involvement of specific components of the basal ganglia in completing these functions. The direct and indirect pathways serve one of two purposes in motor control (Alexander and Crutcher, 1990; Alexander, 1995). First, they could be antagonistic to each other in that they scale or brake the intended movement if the two pathways project to the same neurons in the internal globus pallidus and substantia nigra pars reticulata, or the two pathways could project to

different parts of the internal globus pallidus and substantia nigra pars reticulata. In the latter formation the two pathways complement each other in an 'inhibitory surround' fashion by reinforcing the intended motor pattern (via the direct pathway) and suppressing conflicting motor patterns (via the indirect pathway) (Alexander and Crutcher, 1990; Alexander, 1995). The putamen influences motor control through preparatory (target perception in space) and execution (direction of limb movement and temporal muscle activation patterns) aspects of motor control (Alexander and Crutcher, 1990; Alexander, 1995). A recent review of the literature on basal ganglia research has pointed to a more central role of the external globus pallidus and subthalamic nucleus in the role of movement (Chesslet and Delfs, 1996). These nuclei were originally thought of as just relay centers for information from the striatum (Albin et al., 1989). However, output of the external globus pallidus and subthalamic nucleus have been related to motor anomalies found in major movement disorders like Parkinson and Huntington Disease (Chesslet and Delfs, 1996).

A.1.4 The Corpus Callosum and Interhemispheric Interaction in Motor Control

The two cerebral hemispheres are interconnected by the largest fibre bundle in the brain called the corpus callosum (Figure 5). Over 300

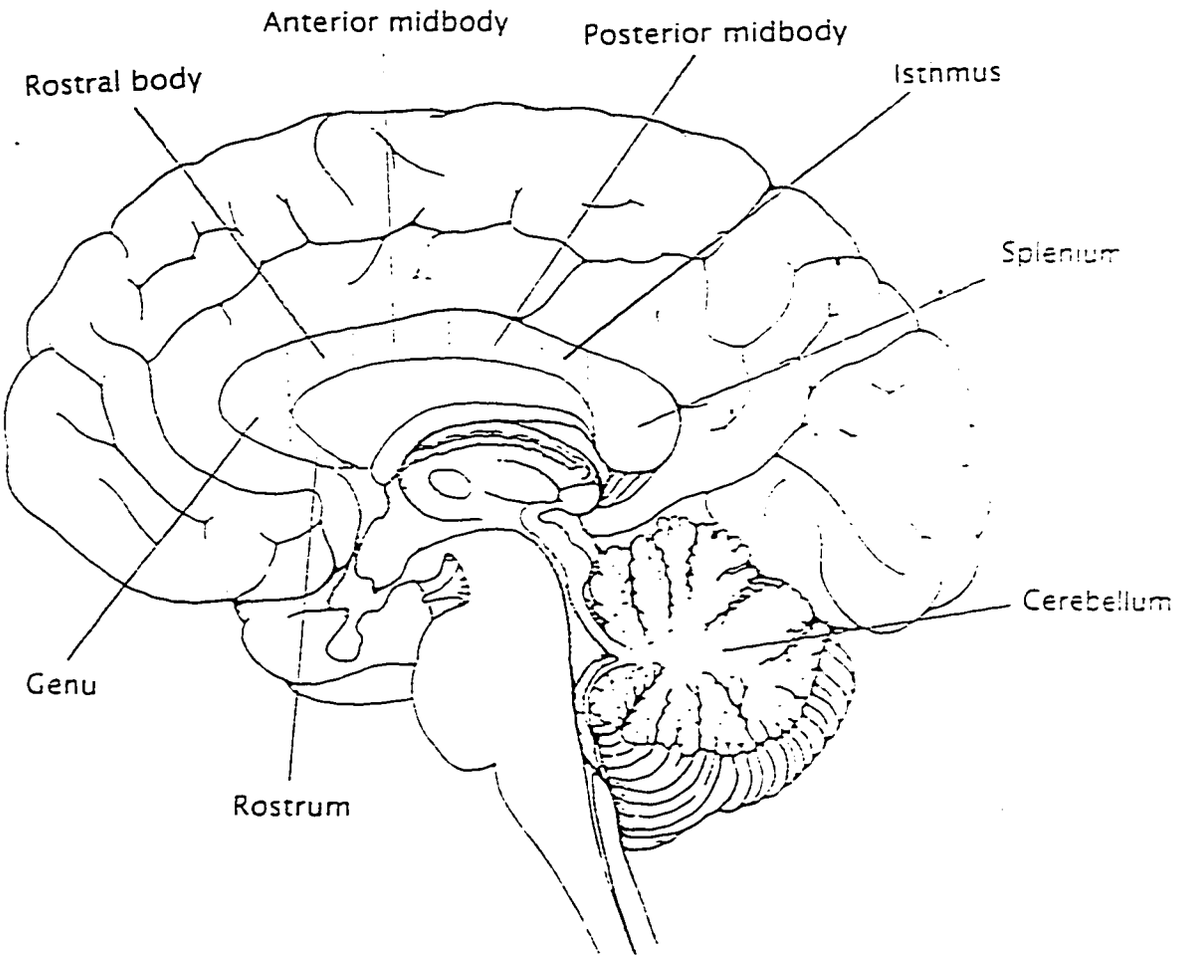


Figure 5. A mid-sagittal section of the human brain showing the cerebellum and the seven sections of the corpus callosum (adapted from Martin and Jessel, 1991).

million axons that connect homologous cortical structures to each other make up the corpus callosum (Nolte, 1993). The corpus callosum can be divided into sections each containing fibres that interconnect distinct parts of the cerebral cortex. The rostral inferior termination of the corpus callosum is called the rostrum. This portion of the corpus callosum interconnects the caudal/orbital prefrontal and inferior premotor cortices (Geidd et al., 1994). The most rostral end of the corpus callosum is called the genu that interconnects prefrontal cortices (Geidd et al., 1994). Going caudally back from the genu is the rostral body. This section interconnects the premotor cortex, supplementary motor area, prefrontal, and anterior cingulate cortices (Geidd et al., 1994; Steere and Arnsten, 1995). The anterior and posterior midbodies are the next two corpus callosum regions that interconnect the motor and somatosensory cortices respectively (Geidd et al., 1994). Caudal from the posterior midbody is the isthmus. The isthmus interconnects the superior temporal and posterior parietal cortices (Geidd et al., 1994). The most caudal section of the corpus callosum is the splenium. This section interconnects the occipital and inferior temporal parts of the cerebral cortex (Geidd et al., 1994). In general, the main role of the corpus callosum is to provide a means of communication between the two hemispheres (Nolte, 1993). The question of how transfer of information between hemispheres by the

corpus callosum influences motor behavior has been the focus of many studies (Netz et al., 1995; Meyer et al., 1995; Geffen et al., 1994; Sauerwein and Lassonde, 1994; Aglioti et al., 1993). In bilateral movements, the corpus callosum is thought to inform each hemisphere of the output of the other (link corollary discharge of the motor cortices) and assist in the transfer of feedback from the senses (Geffen et al., 1994). The anterior corpus callosum relays corollary motor feedback while sensory feedback information is transferred through the posterior callosum (Geffen et al., 1994). In unilateral movement, the corpus callosum is responsible for the transfer of lateralized information (covered in the next section) (Geffen et al., 1994) and interhemispheric inhibition (Geffen et al., 1994; Netz et al., 1995; Meyer et al., 1995) or excitation during motor output (Meyer et al., 1995).

It is widely known that the cerebral hemispheres control movement on the contralateral side of the body due to the decussation of the corticospinal tracts before leaving the brain (Ghez, 1991c). Recent studies have found that there is *bilateral* hemisphere activation during unilateral movement (Kawashima et al., 1993; Li et al., 1996; Netz et al., 1995; Meyer et al., 1995; Pulvermüller et al., 1995). From initially bilaterally generated movements, one hemisphere is blocked from

sending output down the corticospinal tract through inhibitory signals in the form of corollary motor discharge (Geffen et al., 1994; Netz et al., 1995; Meyer et al., 1995). The result is transcallosal inhibition of bilateral motor output to produce a net unilateral movement (Netz et al., 1995; Meyer et al., 1995). Also, there is evidence for facilitation across the corpus callosum (Meyer et al., 1995). Interhemispheric communication via the corpus callosum is not directly responsible for transferring explicit motor commands. The information transferred is related more to premotor planning of movement (Netz et al., 1995; Meyer et al., 1995; Geffen et al., 1994; Sauerwein and Lassonde, 1994; Aglioti et al., 1993). By providing a means of communication between hemispheres, the corpus callosum plays a major role in the control of movement.

A.1.5 Cerebral Dominance in Motor Control

Cerebral dominance has been determined for a variety of functions including language, consciousness, and perceptual processes (Kawashima et al., 1993; Geschwind and Galaburda, 1985; Geschwind, 1984; Galaburda, 1984). For example, 95-98% of right handed subjects show left hemisphere dominance for language (Netz et al., 1995; Kupfermann, 1991). In studying the pattern of hemispheric activation during movement, researchers have postulated

that there is a dominant hemisphere for motor function as well (Netz et al., 1995; Geffen et al., 1994; Kawashima et al., 1993). Researchers have found that right-handed subjects demonstrate a left-hemisphere dominance for motor control as well as language (Netz et al., 1995; Meyer et al., 1995). It is thought that the left hemisphere may have exclusive control over some movements regardless of the hand being used (Geffen et al., 1994). However, constant feedback from the senses (via interhemispheric communication) is still required for accuracy and timing of actions (Geffen et al., 1994). One major reason interhemispheric transfer is required in movement is because of the lateralization of information processing in the human brain (Geffen et al., 1994). Verbal and temporal information are lateralized to the left hemisphere while visuospatial information is lateralized to the right hemisphere (Geffen et al., 1994). Therefore, if a response is to be made with the right hand, information regarding the visuospatial aspects of the response would be transferred through the corpus callosum to the left hemisphere which provides motor output for the right side of the body.

A.1.6 Morphological Cerebral Asymmetries and Motor Control

From the functional asymmetry in the brain the next question would be: "Are there any structural asymmetries in the brain that correlate

with these behavioral asymmetries?" The brain is not a structurally symmetrical organ. In fact many structures show significant asymmetry between the right and left sides of the brain. Cerebral asymmetry has been found as early as 29-31 weeks of gestational age (Geschwind, 1984; LeMay, 1984; Netz et al., 1995). Areas of the motor system demonstrating asymmetry include the frontal lobes and caudate nuclei (Galaburda, 1984; LeMay, 1984; Duara et al., 1991; Hynd et al., 1990; Castellanos et al., 1994. 1996; White et al., 1994; Foundas et al., 1995a, 1995b, 1996). These areas are typically larger on the right side as compared to the left (show a right greater than (>) left asymmetry). Other structures typically show the opposite, left > right asymmetry in the human brain. These structures include the putamen (Aylward et al., 1996; Castellanos et al., 1996) and globus pallidus (Singer et al., 1993; Peterson et al., 1993a, 1993b; Aylward et al., 1996; Kooistra and Heilman, 1988; Orthner and Sendler, 1975).

Some researchers have related the findings of cerebral asymmetry to asymmetry in motor preference or handedness (Kooistra and Heilmann, 1988, White et al., 1994, Foundas et al., 1995a, 1995b, 1996). White et al. (1994) found a leftward asymmetry of the motor region of the frontal lobe (motor cortex). They related this finding to

the predominance of right-handed people in the population (handedness was not directly assessed in this study). Foundas et al. (1995a, 1995b, 1996) assessed handedness and asymmetry of frontal motor structures. They found a strong relationship between the leftward asymmetry of these structures and right-handedness of the subjects. The study by Kooistra and Heilman (1988) related the asymmetry of the globus pallidus to handedness in the population. From the research described above, it is evident that asymmetry of motor structures in the human brain does have an impact on outward motor patterns.

A.2 Neuroimaging Studies on ADHD

Two types of neuroimaging are available to researchers. Structural neuroimaging provides researchers a view of the inside of the body. In essence, this type of imaging provides researchers with a picture of the inside of the body without the need for dissection. Two methods of structural imaging have been employed in the study of ADHD. These methods are computed tomography (CT) and magnetic resonance imaging (MRI). Dynamic imaging, on the other hand, allows researchers to observe how the brain operates. Two types of dynamic neuroimaging techniques used to study ADHD are single-photon emission computed tomography (SPECT) and positron emission

tomography (PET). In using these methods, researchers have made discoveries concerning the question of how neural structure and function in ADHD subjects differs from the normal population.

A.2.1 Structural Brain Imaging

A.2.1.1 Computed Tomography (CT) Findings

The majority of studies that used CT to compare neural structure between ADHD and normal controls have found no significant differences in any neural structures (Shaywitz et al., 1983; Harcherick et al., 1984; Lou et al., 1984, 1989, 1990; Seig et al., 1995; Thompson et al., 1980). The main reason for this is probably due to the technological limitations of CT. However, some early studies using CT to analyze young adult subjects with hyperkinesis and minimal brain dysfunction (an early diagnosis of ADHD) found evidence of mild to moderate cortical atrophy as evidenced by sulcal widening (Nasrallah et al., 1986). Another study found cerebroventricular dilation in four subjects diagnosed with attention deficit disorder (an early label for ADHD) (Caparulo et al., 1981). The relatively poor resolution of CT is unable to detect the differences that have been found in ADHD subjects with more advanced imaging technologies like MRI.

A.2.1.2 Magnetic Resonance Imaging (MRI) Findings

MRI studies have uncovered abnormalities in neural structure in ADHD probands. Differences in structure have been uncovered in the basal ganglia (Castellanos et al., 1994, 1996; Singer et al., 1993; Denckla et al., 1991), corpus callosum (Semrud-Clikeman et al., 1994; Giedd et al., 1994; Lyoo et al., 1996; Baumgartner et al., 1996), cerebral hemispheres (Castellanos et al., 1994, 1996; Hynd et al., 1990), and other structures like the cerebellum (Castellanos et al., 1996) and lateral ventricles (Hynd et al., 1990; Denckla et al., 1991).

Studies that have measured the cerebral hemispheres of ADHD subjects have generally found reduced brain volume in comparison to normal controls (Castellanos et al., 1994, 1996). The difference in total brain volume is approximately 5% (Castellanos et al., 1994, 1996). In comparing specific regions of cortex, a prominent reduction of frontal lobe volume is significant in ADHD subjects (Hynd et al., 1990; Castellanos et al., 1994, 1996). Whereas normal subjects show a larger right frontal lobe (LeMay, 1984), ADHD subjects demonstrate a significantly smaller right anterior frontal cortex (Hynd et al., 1990; Castellanos et al., 1996). As a result the right>left cerebral hemisphere asymmetry generally found in normal subjects (LeMay, 1984; Duara et al., 1991; Hynd et al., 1990; Castellanos et al., 1996) is

significantly less pronounced in ADHD probands (Castellanos et al., 1996).

The significance of frontal lobe alteration in ADHD was shown in a study examining the ability to predict group membership for children with developmental disorders based on neural structures (Semrud-Clikeman et al., 1996). This study found that three regions of cerebral cortex; the right anterior frontal region, left insula, and left planum temporale, were most useful in discriminating between normal control, dyslexic, and ADHD subjects.

Morphometric analysis of the basal ganglia has concentrated on three regions, the caudate nucleus, putamen, and the globus pallidus. These three regions comprise the bulk of the basal ganglia. A region known as the lenticular nucleus has also been measured in basal ganglia morphometry. This region is actually the combination of the putamen and globus pallidus.

Early structural neuroimaging studies on the caudate nuclei revealed a unique and somewhat confusing picture of ADHD. Denckla et al. (1991) found that the caudate nuclei in ADHD subjects were significantly larger than in controls. A study by Hynd et al. (1993),

however, found that the left caudate nucleus is significantly smaller in ADHD subjects. The smaller left caudate nucleus contributed to a right>left caudate nucleus asymmetry in ADHD subjects which was opposite to the 'normal' left>right caudate nuclear asymmetry shown in the control group. In another study measuring basal ganglia volumes in ADHD, no caudate nucleus asymmetry (hence, caudate nucleus symmetry) was found in ADHD and normal control subjects (Aylward et al., 1996). However, other studies measuring caudate nuclear volume in a large number of subjects (n=50) have called these findings into question. It has been shown in studies by Peterson et al.(1993a, 1993b) and Castellanos et al. (1994, 1996) that normal asymmetry of the caudate nuclei is right>left rather than left>right as demonstrated in Hynd et al.'s control group. As for ADHD subjects, a significantly smaller right caudate nucleus causes a significant lack of normal caudate asymmetry rather than the right>left asymmetry found by Hynd et al. (1993) (Castellanos et al., 1994, 1996). In ADHD subjects, the smaller right caudate nucleus was not significantly different in volume from the left caudate, unlike normal subjects that demonstrated right>left asymmetry (Castellanos et al., 1994, 1996). It was also found in these later studies that total volume of the caudate nuclei does not differ between ADHD and control subjects (Castellanos et al., 1996). This finding contrasts with the previous finding of larger

caudate nuclei in ADHD (Denckla et al., 1991). The later studies carry more statistical power as the number of subjects is substantially larger (50 vs. 8).

Examination of putamen volumes has found that ADHD subjects do not differ from the left>right putamen asymmetry found in normal controls (Castellanos et al., 1996; Aylward et al., 1996). An examination of putamen volumes in ADHD subjects with comorbid Tourette syndrome found that these subjects show a reduced left putamen volume (Singer et al., 1993). Looking at the globus pallidus, reductions in pallidal volume have been found bilaterally in ADHD subjects (Castellanos et al., 1996; Aylward et al., 1996) and on the left side in ADHD subjects (Aylward et al., 1996) and in ADHD subjects with comorbid Tourette syndrome (Singer et al., 1993). In both studies on pure ADHD subjects, a reduction in the normal left>right pallidal asymmetry was found. For the lenticular nuclei, no difference in size or asymmetry was found between ADHD and control subjects (Castellanos et al., 1996). However, for ADHD subjects with Tourette syndrome mean asymmetry was reversed as compared to control subjects (Singer et al., 1993). This finding was due to a larger right and smaller left lenticular nuclei in comorbid ADHD subjects (Singer et al., 1993). It was suggested by Aylward et al. (1996) that alteration

in globus pallidus volumes are associated with ADHD in particular while changes in lenticular nucleus volume are associated with Tourette syndrome in particular.

Early studies on corpus callosum morphology in ADHD revealed smaller measures of the genu and splenium in ADHD subjects (Hynd et al., 1991). Numerous other studies have examined the corpus callosum in ADHD and have revealed significant differences either in the anterior callosum regions (Baumgartner et al., 1996; Geidd et al., 1994), posterior callosum regions (Lyoo et al., 1996; Semrud-Clikeman et al., 1994), or no significant differences at all (Castellanos et al., 1996). Findings in the posterior callosum show significantly smaller measures of the splenium (Lyoo et al., 1996; Semrud-Clikeman 1994) or isthmus (Lyoo et al., 1996) in ADHD subjects. Anterior differences in the corpus callosum have been found in the rostrum (Geidd et al., 1994) and rostral body (Baumgartner et al., 1996; Geidd et al., 1994).

Other morphometric measures have been taken from the brains of ADHD patients and compared to normal controls. Measures of ventricular volume have shown either no differences in total volume (Castellanos et al., 1996) or larger ventricles (Denckla et al., 1991). Larger posterior lateral ventricles (Lyoo et al., 1996), and a smaller left

lateral ventricle (Castellanos et al., 1996) have also been found in ADHD subjects. One other potentially important finding with respect to motor control is the smaller cerebellar volume found in ADHD subjects (Castellanos et al., 1996).

A.2.2 Dynamic Brain Imaging

A.2.2.1 Single-Photon Emission Computed Tomography (SPECT) Findings

The first studies of dynamic brain imaging in ADHD were performed in Denmark by Hans Lou and his colleagues (1984, 1989, 1990). In these studies ADHD children were compared to normal children on measures of regional cerebral blood flow (CBF) at rest with open eyes. SPECT images were taken in a plane 50mm above the orbitomeatal line (a line from the middle of the eye to the middle of the ear) to include the prefrontal cortex, presylvian regions, striatum (basal ganglia), diencephalon, and occipital cortex.

Lou et al.'s first study (1984) measured CBF in a heterogeneous group of ADHD children, most of which had comorbid conditions (i.e.: dysphasias, visuospatial neurological deficits, mild mental retardation) and/or suffered pre- or perinatal neural trauma. All SPECT scans of ADHD subjects showed central hypoperfusion of the mesial frontal

lobe. Dysphasic or control subjects did not demonstrate this characteristic on SPECT scans. Also, the majority of ADHD subjects demonstrated bilateral hypoperfusion of the caudate nuclei region. The occipital lobes of ADHD subjects were relatively hyperperfused.

In the following studies (Lou et al., 1989, 1990) pure ADHD subjects were analyzed separately from ADHD subjects with comorbid conditions. Comparisons with non-age or sex matched control groups in both studies found, for pure ADHD subjects, significant hypoperfusion in the right striatum (Lou et al., 1989), both striata and posterior periventricular regions (Lou et al., 1990). The occipital lobe (Lou et al., 1989, 1990), left sensorimotor and primary auditory regions demonstrated significant hyperperfusion in pure ADHD subjects (Lou et al., 1989). The results of ADHD plus comorbid conditions scans closely match those of pure ADHD subjects with the exception that significant hyperperfusion was found in the occipital lobes but not in the sensorimotor and primary auditory regions (Lou et al., 1989).

The effects of methylphenidate (Ritalin®), a drug commonly used to manage ADHD, on CBF have been examined in two SPECT studies (Lou et al., 1984, 1989). Generally, these studies show that the

anomalous CBF demonstrated in ADHD subjects is normalized following methylphenidate administration. Increased perfusion was shown in central brain regions (mesencephalon and basal ganglia) while sensory and motor areas showed decreased perfusion (Lou et al., 1984). More precisely, significant increases in blood flow have been found in both posterior periventricular regions and to the right striatum (Lou et al., 1989). The asymmetry of drug action in the striatum was an unexpected finding and the authors indicated that it may reflect more permanent type of damage in the right striatum in ADHD (Lou et al., 1989).

In summary, the findings from Lou et al. (1984, 1989, 1990) show that there is aberrant blood flow in the brains of people with ADHD. Hypoperfusion has been found in the frontal and central (striatal and posterior periventricular) regions, while hyperperfusion has been found in the occipital lobes and sensorimotor and primary auditory cortices. Also, administration of medication commonly used to manage ADHD normalizes blood flow to affected areas in ADHD subjects. These findings have been questioned by other researchers because of small sample sizes and the high prevalence of early neurological insult in the ADHD subject population (ranging from 38% to 83% of subjects) (Zametkin et al., 1993).

More recent SPECT studies on children with ADHD have revealed similar findings to those described by Lou et al. (1984, 1989, 1990). A study of 54 ADHD subjects found that 65% demonstrated significant prefrontal cortex deactivation at rest in response to intellectual challenge (versus 5% of the control group) (Amen et al., 1993). Of the 35% that did not show this reaction, 63% demonstrated significantly lower baseline prefrontal cortex activation versus control subjects. In summary, 87% of ADHD subjects demonstrated low prefrontal activity (Amen et al., 1993).

The asymmetry of SPECT tracer uptake has also been studied in ADHD subjects (Seig et al., 1995). A right > left asymmetry in uptake was noted globally and in the frontal, temporal, and parietal regions in ADHD children. The greatest asymmetry was found in the frontal and temporal regions. The right > left asymmetry in ADHD subjects significantly differed from control subjects who show a global left > right asymmetry globally and in the frontal and parietal regions. There was no difference in asymmetry between ADHD and control subjects in the temporal region as both groups demonstrated a right > left asymmetry (Seig et al., 1995).

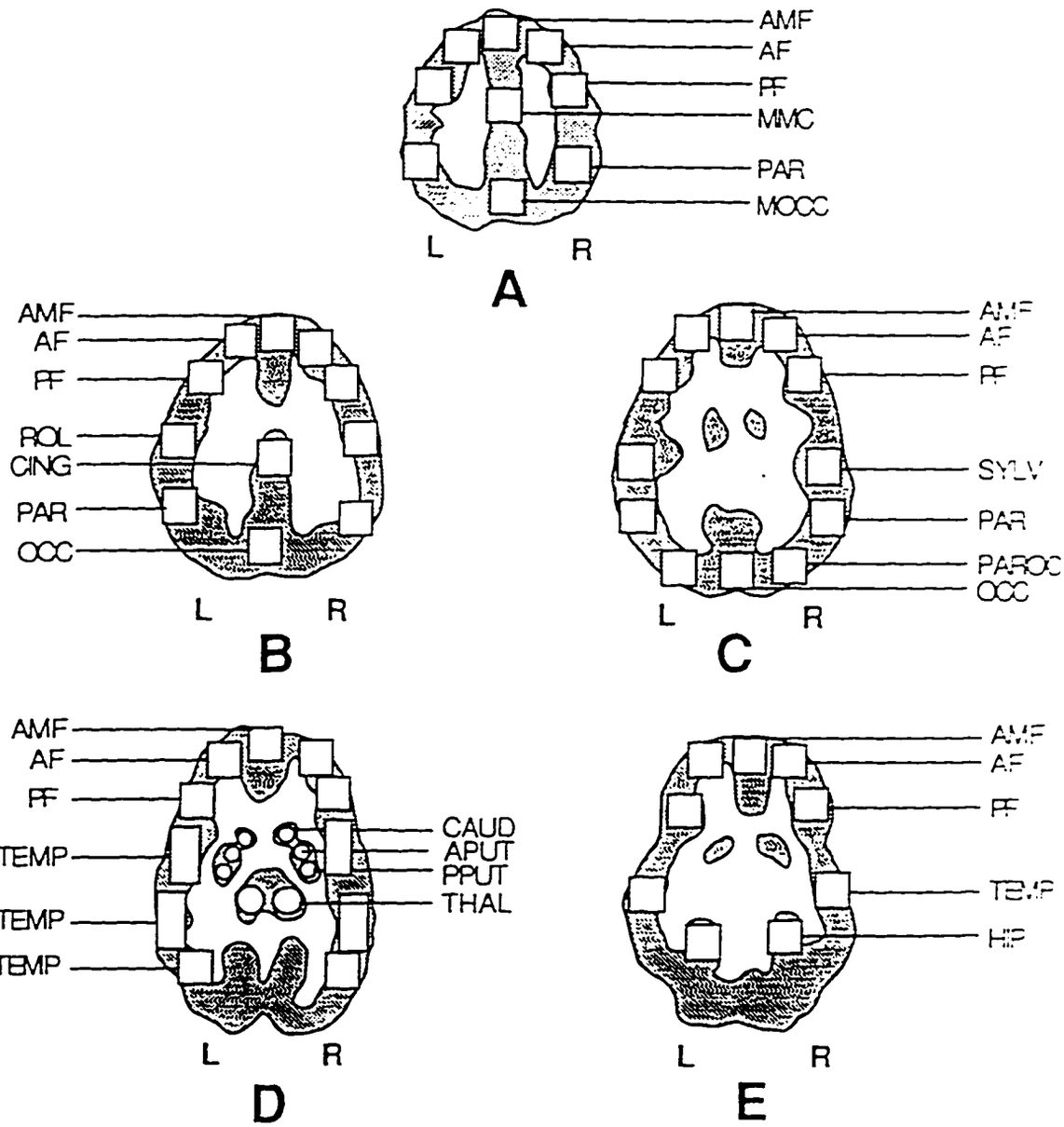
All SPECT studies on ADHD have found aberrant blood flow in ADHD probands. The common findings in these studies have been a reduced frontal and central activity including the basal ganglia and overactivity in the occipital lobes and sensorimotor and primary auditory regions. Further inquiry into brain metabolism in ADHD subjects has been completed with the higher resolution of PET.

A.2.2.2 Positron Emission Tomography (PET) Findings

A unique picture of ADHD has been developed through PET studies. However, due to issues of safety around radiation exposure to children, most studies using PET to study ADHD have focused on adolescents and adults.

All published PET research on ADHD has been performed by Allan Zametkin and his colleagues at National Institutes of Health, USA (Zametkin et al., 1989, 1993; Matochik et al., 1993, 1994; Ernst et al., 1994a, 1994b). These studies used radioactive glucose ([^{18}F] flouro-2-deoxy-D-glucose) to measure cerebral glucose metabolism (CMR_{glu}) while subjects performed an auditory attention task (continuous performance test) with their eyes closed. Measurements of CMR_{glu} were taken from 60 regions of interest in five different planes of tissue (Figure 6). Three measures of CMR_{glu} were determined in the PET

Figures 6A-6E. Template of regions of interest. A through E correspond to the 5 axial planes chosen for analysis of the results: A plane at 94 mm above the cantheomeatal line, B plane at 84 mm, C plane at 67 mm, D plane at 53 mm, and E plane at 40 mm. L = left, R = right; AF = anterior frontal, AMF = anterior medial frontal, APUT = anterior putamen, ATEMP = anterior temporal, CAUD = caudate, CING = middle cingulate, HIP = hippocampus, MMC = middle medial cortex, MOCC = medial occipital, MTEMP = middle temporal, OCC = occipital, PAR = parietal, PAROCC = parietal occipital, PF = posterior frontal, PPUT = posterior putamen, PTEMP = posterior temporal, ROL = rolandic, SYLV = sylvian, TEMP = temporal, THAL = thalamus.


AMF
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studies. Absolute regional CMR_{glu} is the 'raw score' of a specified region of interest. Global CMR_{glu} is an average of absolute regional CMR_{glu} for all 60 regions of interest. Finally, normalized regional CMR_{glu} scores are calculated by dividing the absolute CMR_{glu} score for a specific region of interest by the global CMR_{glu} score for the individual (Zametkin et al., 1990).

The first PET study on ADHD (Zametkin et al., 1990) examined a mixed sex group of ADHD adult subjects meeting the diagnostic criteria for ADHD (DSM-III and Utah criteria [Wender et al., 1981]). These adults were biologic parents of children with ADHD, and had never been treated with stimulants. Statistical comparison of ADHD subjects to a control group found a significant reduction in global CMR_{glu} in ADHD probands by 8.1%. Also, significant reductions in absolute CMR_{glu} were found in 30 of 60 regions of interest for ADHD subjects. Four of the 60 regions of interest, primarily located in the premotor and somatosensory cortex (Table 2), remained significantly depressed in ADHD subjects when CMR_{glu} values were normalized. The presence of learning disorders in the ADHD group and effects of sex did not influence the significance of these findings (Zametkin et al., 1990).

A later study (Zametkin et al., 1993) comparing adolescent ADHD and control groups found no significant differences in absolute or global CMR_{glu}. However, ADHD subjects exhibited reduced normalized CMR_{glu} in six regions and higher CMR_{glu} in one region (Table 2). Of note is the reduced CMR_{glu} in the left anterior frontal region of plane B that also showed reduced CMR_{glu} in ADHD adults (Zametkin et al., 1990). In comparing male-only subgroups of subjects, five of the seven regions, including the left anterior frontal region of plane B, were found significantly different while two different regions demonstrated a difference (Table 2). Comparison of the female only subgroups found no significant differences in global, absolute, or normalized CMR_{glu} even though there was a 17.6% difference in global CMR_{glu} between ADHD and control females. The lack of significance was attributed due to the low numbers of females compared in this study (n=3).

A later PET study that included more female subjects found no statistically significant differences in global or absolute CMR_{glu} between mixed sex groups (Ernst et al., 1994b). ADHD subjects showed significant increases of CMR_{glu} in two regions but authors of this study attributed these differences to random variation (type I error) as the significance level (α level) of $p<.05$ was not adjusted for

Table 2: Brain regions found to be altered in ADHD subjects on PET scans and Regions showing altered metabolism after stimulant medication administration to ADHD subjects.

L- left; R- right; M- methylphenidate; D- dextroamphetamine
+ - effect size of >.8 standard deviation
*- significantly different ($p<.05$) from pre-drug state

1- Zametkin et al., 1990; 2- Zametkin et al., 1993 (all subjects); 3- Zametkin et al., 1993 (males only); 4- Ernst et al., 1994b (pooled results); 5- Ernst et al., 1994b (males only); 6- Ernst et al., 1994b (females only); 7- Matochik et al., 1993; 8- Matochik et al., 1994; 9- Ernst et al., 1994a

PLANE	*ADHD<CONTROL*	*ADHD>CONTROL*	*INCREASED CMR_{glu}*	*DECREASED CMR_{glu}*
A	L. Posterior Frontal[1]	NONE	L. Posterior Frontal(M*)[7]	NONE
	L. Parietal [3]		L. Anterior Medial(M*)[7]	
B	Anterior Medial Frontal[1]	L. Posterior Frontal[2,4]	Anterior Medial Frontal(M*)[7]	R. Rolandic(D*)[7]
	L. Anterior Frontal[1,2,3,4,5]	L. Occipital[3]	L. Anterior Frontal(M*)[7]	Occipital(D*)[7]
	L. Rolandic[1]		R. Rolandic(M*)[7]	
			R. Parietal(M*)[7]	
			L. Posterior Frontal(M*)[7]	
			L. Parietal(M*)[7]	
C	NONE	NONE	Anterior Medial Frontal(D*)[7]	Anterior Medial Frontal(M*)[7]
			R. Parietal(D*)[9]	L. Parietal(M*)[7]
				L. Parieto-Occipital(M*)[7]
				Occipital(M*)[7]
				R. Posterior Frontal(M*)[7]
				R. Parietal(M*)[7]
				L. Anterior Frontal(D*)[7]
D	R. Posterior Temporal[2,3,4]	NONE	L. Posterior Putamen(M*)[7]	L. Anterior Frontal(D*)[7]
	L. Thalamus[2,3]		R. Posterior Temporal(D*)[7]	R. Anterior Frontal(D*)[7]
			R. Thalamus(D*)[7]	R. Anterior Putamen(M*)[8]
			R. Caudate(D*)[7]	R. Anterior Temporal(D*)[9]
			R. Posterior Frontal(D*)[7]	
			R. Anterior Temporal(D*)[7]	
			Medial Temporal(D*)[7]	
E	R. Temporal[2,3]	NONE	R. Posterior Frontal(M*)[8]	L. Temporal(M*)[7]
	L. Posterior Frontal[2,3]			R. Posterior Frontal(D*)[7]
	R. Hippocampus[2,6]			L. Anterior Frontal(D*)[7]
				Anterior Medial Frontal(D*)[7]
				R. Anterior Frontal(D*)[7]
				R. Hippocampus(D*)[9]

the numerous comparisons performed (Ernst et al., 1994b). To increase statistical power, results from this study were pooled with the previous study on adolescents (Zametkin et al., 1993) and re-analyzed. No significant differences were found in global or absolute CMR_{glu} in this analysis. However, normalized CMR_{glu} data showed significant reductions in the left anterior frontal (plane B) and right posterior temporal (plane D) in ADHD subjects. Also, higher normalized CMR_{glu} was found in the left posterior frontal (plane B) in ADHD subjects (Table 2).

Analysis of sex subgroups revealed significantly lower global CMR_{glu} in ADHD females as compared to normal females (by 15%) and to ADHD males (by 19.7%). This female subgroup showed a significant reduction in absolute regional CMR_{glu} in 27 of 60 regions of interest compared to normal females and 47 of 60 regions of interest compared to ADHD males. The regions of interest in question were predominantly located in the temporal, premotor, and orbital frontal cortices. No other differences in absolute or global CMR_{glu} were found between ADHD and control subjects in any subgroups (Ernst et al., 1994). For normalized CMR_{glu} values, the anterior medial frontal and left Rolandic regions of plane B were significantly increased for ADHD females compared to ADHD males. When compared to normal

females, ADHD females only differed in the right hippocampal region on normalized CMR_{glu}. In the male subgroup, four regions (three not specified) including the left anterior frontal region of plane B were significantly reduced in ADHD subjects. No other differences were noted in normalized CMR_{glu} between groups.

As methylphenidate (Ritalin®) and dextroamphetamine (Dexedrine®) both can dramatically improve behavioral functioning of ADHD patients, the influence of these stimulant medications on CMR_{glu} in adult ADHD was examined with PET. Acute administration of oral doses of dextroamphetamine and methylphenidate administration changed normalized CMR_{glu} in seven and five of 60 regions of interest respectively (Matochik et al., 1993). Sixteen regions, for both methylphenidate and dextroamphetamine, showed differences of >.8 standard deviations ("a 'large' effect size") between pre- and post-drug conditions (Table 2). Close examination of these results shows that there is no symmetry in action for either medication. The influence of methylphenidate is primarily found in superior regions (planes A-C), while the dextroamphetamine influence is primarily in the lower brain (planes D and E). Of note is the finding that three of the four regions of interest found to show decreased CMR_{glu} in the first PET study on adults (Zametkin et al., 1990) were increased after methylphenidate

administration (Matochik et al., 1993). However, the authors of this research have noted that these results resemble the effect profile of normal subjects administered these same medications (Matochik et al., 1993). It is also of interest that performance on the auditory continuous performance test was improved after dextroamphetamine administration but not methylphenidate administration (Matochik et al., 1993).

The effects of chronic administration of stimulants has also been studied in adults with ADHD (Matochik et al., 1994) but with fewer significant results. Two regions showed significant changes in normalized CMR_{glu} from after chronic administration of methylphenidate. The authors of this study suggest that these two regions, the right anterior putamen of plane D (decrease) and right posterior frontal of plane E (increased), show significance from random variation. Actually, the right posterior frontal region of plane E actually showed the reverse effect (a decrease in CMR_{glu}) in the previous study with *acute* administration of dextroamphetamine (Matochik et al., 1993). The authors also stated that the significance of these results would be lost if an α adjustment was used.

Intravenous dextroamphetamine administration was studied to see if method drug administration has any influence on CMR_{glu} in ADHD subjects (Ernst et al., 1994a). In the small adult sample four subjects showed an increase, two a decrease, and two no change in global CMR_{glu}. Overall, there was no significant difference in either global or absolute CMR_{glu} after drug administration. Three regions did show significant change once CMR_{glu} scores were normalized (Table 2). However, these regions were not among those influenced in previous studies (Matochik et al., 1993, 1994). The authors of this paper state that the failure to replicate the findings of previous studies indicates a high possibility of type I error.

The results of these PET studies show that there are significant differences in brain metabolism between ADHD and control subjects. Studies on the effect of stimulant medications on CMR_{glu} in ADHD give an unclear picture as to the neural mechanism behind ADHD. Authors of this research have suggested that PET may not be the best way to study the effect of stimulant drugs on this disorder (Matochik et al., 1993). Interpretation of the normalized CMR_{glu} results should be conducted with caution as numerous comparisons were performed without any control for type I error. Although researchers in Zametkin's group do offer reasons for not controlling for type I error

(Matochik et al., 1993), they also ascribe many of their aberrant significant findings to 'random variation' (type I error) (Zametkin et al., 1993; Matochik et al., 1994; Ernst et al., 1994a, 1994b).

A.3 Neuropsychological Motor Performance Findings in ADHD

Neuropsychological testing procedures examine brain functions by measuring subject performance on standardized tests. Numerous neuropsychological tests are available to test factors such as overall cognitive ability (intelligence), attentional processes, academic achievement, executive function, and sensorimotor skills (Yeats and Bornstein, 1994; Barkley et al., 1992). Motor skills can be quantifiably measured through various neuropsychological tests. Researchers have found that abnormality of motor structures in the brain and the resulting anomalous hemispheric asymmetry influence motor performance scores (Massman and Doody, 1996).

Tests of motor function that have been used in ADHD subjects vary from questionnaires of motor preference (Edinburgh Handedness Inventory; Oldfield, 1971), repetitions of movements (Time To Do 20; Carte et al., 1996), to tests using specialized equipment to measure motor performance (finger tapping test (FTT); Seidman et al., 1995; grooved pegboard test (GPT); Barkley et al., 1992). Researchers have

not found an excess of non-right motor preference in ADHD subjects (Biederman et al., 1994; Siedman et al., 1995). However, ADHD subjects do show deficits in motor control similar to those with frontal lobe damage (Shue and Douglas, 1992). Specific difficulties arise in poor response inhibition, more echopraxic responses (involuntary imitation of other's movements), problems alternating responses quickly and accurately, and impulsive errors (Shue and Douglas, 1992). Also, slow gross motor output (Carte et al., 1996), greater difficulty in motor tasks (Barkley et al., 1992; Siedman et al., 1995), and more motor 'soft signs' (sensorimotor abnormalities that cannot be localized but indicate subtle brain dysfunction; Aronowitz et al., 1994) have been associated with ADHD. These studies have attributed the difference in motor performance in ADHD subjects to abnormalities in the frontal-striatal motor system in ADHD subjects (Aronowitz et al., 1994; Carte et al., 1996; Shue and Douglas, 1992; Siedman et al., 1995, 1997a).

A.3.1 Performance Asymmetry.

Although motor performance has been studied in detail, performance asymmetry (the difference in performance between hands), is one aspect of motor control in ADHD that has only been examined by a few researchers (Panich et al., 1994; Seidman et al., 1995). Generally,

people perform motor tasks better with one hand than the other hand. This difference in performance between hands is said to be asymmetrical. As a rule, the difference between hands is normally around 10% and performance outside the normal range is indicative of underlying dysfunction (Golden, 1981; Massman and Doody, 1996). How performance asymmetry is determined has been accomplished in different ways in different studies. Four different methods have been used in the literature (laterality quotient, dominance ratio, non-preferred hand score divided by preferred hand score, and preferred minus non-preferred hand scores) and will be briefly described below.

A.3.1.1 The Laterality Quotient

The laterality quotient (LQ) is a ratio of the difference in performance between the hands over the sum of performance of the hands. This measure of performance asymmetry was used by Panich et al. (1994) and a variation of this formula was used by Carlier et al. (1994). The formula for the LQ is as follows:

$$\frac{\text{Preferred Hand Score - Non-preferred Hand Score}}{\text{Preferred Hand Score + Non-preferred Hand Score}} \times 100 = \text{LQ}$$

Hence, a negative LQ would indicate a non-preferred hand dominance while positive scores indicate a preferred hand dominance. Scores

approaching zero indicate nearly equal performance by either hand (a lack of performance asymmetry).

A.3.1.2 The Dominance Ratio

Like the LQ, the dominance ratio (DR) is a ratio of performance scores on a given test. However, the difference between the hand scores, unlike the LQ, is divided only by the preferred hand score. This formula has been used to determine performance asymmetry by many researchers (Andrew, 1981; Seidman et al., 1995; Massman and Doody, 1996). The formula used to calculate the DR is as follows:

$$\frac{\text{Preferred Hand Score - Non-preferred Hand Score}}{\text{Preferred Hand Score}} \times 100 = \text{DR}$$

Hence, a negative dominance ratio would indicate a non-preferred hand dominance while positive scores indicate a preferred hand dominance. Scores approaching zero indicate nearly equal performance (symmetrical performance) by either hand.

A.3.1.3 Other Measures of Performance Asymmetry

Two other measures of performance asymmetry have been used in the literature (Dodrill, 1978; Bornstein, 1986a, 1986b). One measure is the ratio of non-preferred score divided by preferred score (NP/Pr). A

value less than zero indicates a preferred hand dominance while values over zero would indicate a non-preferred hand dominance (Dodrill, 1978; Bornstein, 1986b). The other measure is the difference between preferred and non-preferred hand scores (Pr-NP). In this measure, positive values indicate preferred hand dominance and negative values indicate non-preferred hand dominance (Bornstein, 1986a). Values approaching zero for either formula indicate symmetrical motor performance.

A.3.2 Performance Asymmetry in ADHD

Results of studies of performance asymmetry on ADHD subjects have found significant differences in performance asymmetry from normal controls. A pilot study performed by Panich et al. (1994) found that ADHD subjects had reduced asymmetry in performance on the GPT as compared to normal controls. Seidman et al. (1995) found the opposite for ADHD subjects for the FTT. ADHD subjects demonstrated a greater dominance ratio (more asymmetrical performance) than controls on the FTT. These studies indicate that performance asymmetry is aberrant in ADHD subjects.

A.4 Summary of Introduction and Hypothesis

Studies have found that abnormalities in neural structures responsible for motor control result in changes in observed motor performance (Massman and Doody, 1996). Many researchers have found evidence of deviant neural structure and function in ADHD subjects (Castellanos et al., 1994, 1996; Hynd et al., 1990, 1991; Zametkin et al., 1990, 1993; Lou et al., 1984, 1989, 1990; Seig et al., 1995; Semrud-Celikeman et al., 1994; Geidd et al., 1994; Baumgartner et al., 1996; Lyoo et al., 1996; Denckla et al., 1991; Aylward et al., 1996; Singer et al., 1993; Nasrallah et al., 1986; Caparulo et al., 1981; Amen et al., 1993; Ernst et al., 1994b). Therefore, the changes in the frontal lobes, basal ganglia, and cerebellum, which are all concerned with the control of motor behavior, should be evident in the motor patterns of ADHD subjects. The objective of this study was to see if there is a relationship between the pattern of motor performance on neuropsychological tests and the altered neural structure found in ADHD patients. It was hypothesized that there would be a difference in motor performance measures and/or intermanual difference measures between ADHD and normal control subjects. Other researchers have found altered motor patterns in ADHD subjects using different neuropsychological measures (Shue and Douglas, 1992, Barkley et al., 1992, Carte et al., 1996, Aronowitz

et al., 1994). Based on the findings of these studies, the present study was undertaken to examine the motor patterns of ADHD subjects using different neuropsychological motor tests. In addition to using the FTT and GPT, which have been used in other studies (Barkley et al., 1992, Panich et al., 1994, Seidman et al., 1995), two additional tests, the hand dynamometer (DYN) and Purdue pegboard (PPB), were also used to examine motor performance. It was hypothesized that there would be significant differences in either motor performance, performance asymmetry, or both for ADHD subjects.

B Method

For the present study, approval by the Research Ethics Board (Faculty of Medicine, University of Alberta) for the research protocol used herein was obtained at the outset and retained for the duration of the project (see Appendix A).

B.1 Subjects

A total of 62 subjects (n=30 provisional diagnosis of ADHD, n=32 normal controls), aged 6 to 14, were recruited by letter from a local elementary school or a community attention disorder support group. All subjects were tested off medication(s). Inclusion in the ADHD group was based on analysis of parental behavior ratings and a provisional diagnosis by a physician. Two questionnaires were used to obtain behavior ratings for subject classification. Subjects with scores greater than 1.5 standard deviations from the mean on the attention scale of the Child Behavior Checklist (CBCL; Achenbach, 1991) or on the hyperkinesis index of the Revised Conners Parent Rating Scale (CPRS-R; Goyette et al., 1978) were classified as ADHD (Chen et al., 1994). Twenty-six children met these criteria for ADHD (24 males, 2 females) and the 34 children (24 males, 10 females) that did not meet these criteria served as controls. Two children were dropped from the study due to inconsistencies in data collection. Female subjects were

excluded from data analysis due to the low number of ADHD females (n= 2). The resulting groups both had 24 male subjects with a mean age of 9.63 years (control) and 9.95 years (ADHD).

Preferred hand usage was determined by using selected items from the Edinburgh Handedness Inventory (Oldfield, 1971). Subjects were asked which hand was preferred in writing, drawing, throwing, using a toothbrush, spoon, scissors, and a racquet. All of these items have been shown to adequately represent a person's hand preference (Oldfield, 1971; Raczkowski et al., 1974; Bryden, 1977; Williams, 1986; Coren and Porac, 1978; Porac and Coren, 1981). Subjects were dichotomized into those with a right hand preference (score greater than zero) and left hand preference (score less than zero). The distribution of handedness in the test groups was as follows: ADHD: left, n= 4; right n= 20; Control: left, n= 3; right, n= 21.

B.2 Motor Performance Test Administration Procedures

B.2.1 Hand Dynamometer

The hand dynamometer (DYN; Lafayette Instrument Co., P. O. Box 5729, Lafayette, IN, 47903) is a hand-held device that provides a measure of grip strength in kilograms. The procedure described here

is based on Trites (1977) with the exception that the dynamometer used measured only to 50 kilograms rather than 100 kilograms.

In order for the subject to have a firm grip on the dynamometer, the handle was adjusted to fit the subject's hand before testing. Standing in front of the experimenter, the subject would hold the dynamometer in their dominant hand, point it to the floor, squeeze the handle as hard as possible and then release. The experimenter would then take the dynamometer from the subject, record the measure from the device, reset the indicator, and place the device in the subject's other hand. This procedure was completed twice for each hand. If the measures were not within 3 kilograms of each other for one hand, the entire procedure would be repeated again later in the session. In the event that this happened, all four scores per hand would be averaged for a total grip strength score.

B.2.2 Finger Tapping

The finger tapping test (FTT; Reitan Neuropsychology Laboratory, 2920 S. 4th Ave., Tucson, AZ, 85713-4819) consists of a lever mounted to a manual counter that is fixed on a flat board. It is a measure of tapping speed from the Halstead-Reitan Neuropsychology Battery. The procedure described here was adapted from Trites (1977). The

subject was seated at a table across from the researcher with the FTT in a comfortable position paced at the midline of the body. For subjects eight years of age and younger, an electric FTT (with an electric rather than manual counter) was used to record tapping speed. Subjects older than eight years old were tested with the manual FTT. The subject was told that the objective of the test was to press the metal key using their index finger for as many times possible in a small time period (which remained unknown to the subject for the duration of the testing period). It was explained that the index finger should be used to tap while their hand and remaining fingers were kept flat on the table. The subject was also warned that they must fully depress the key on the finger tapping device or else the counter would not register the tap. One practice trial was performed with each hand before measurements were recorded. Ten second trials, timed by the researcher with a stopwatch, would start by the researcher saying 'Start' and end by the researcher saying 'Stop.' The researcher paid close attention to any taps after the trial ended or any abnormalities in manual registration of the tap score by the counter. Three trials in succession were performed on each hand, alternating between hands, until five scores within a range of five were obtained or until ten total trials were completed. In the event that the 'five

within five' criteria was not fulfilled, the top five scores were averaged for the measure of tapping speed.

B.2.3 Grooved Pegboard

The grooved pegboard test (GPT; Lafayette Instrument Co., P. O. Box 5729, Lafayette, IN, 47903) consists of a board with 25 keyhole-shaped holes in various orientations and is a measure of finger dexterity. The procedure described here was adapted from Trites (1977). The GPT was placed on the table in front of the subject with the peg tray closest to the researcher. When using their right hand, subjects filled all of the rows of the pegboard from left to right starting with the top row. The subjects filled the rows from right to left when using their left hand. A non-timed practice trial was given for each hand that consisted of subjects filling the first row (five pegs) of the pegboard. For the test, subjects were instructed to fill in the entire pegboard (25 holes) as quickly as they could using only one hand. For subjects 8 years of age and younger, the time taken to complete the first two rows (ten holes) is the measure most commonly used in neuropsychological evaluation. However, *all* subjects completed the *entire* board for the present study.

The amount of time taken to fill each row, total time to fill board, and errors committed during the test (wrong direction of filling, dropped peg, or help with other hand) were recorded by the researcher.

B.2.4 Purdue Pegboard

The Purdue pegboard (PPB; Lafayette Instrument Co., P. O. Box 5729, Lafayette, IN, 47903) consists of a board with two columns of 25 round holes. Like the GPT, the PPB is a measure of finger dexterity. The testing procedures discussed here for right, left, and both hands are based on Tiffin and Asher (1948). In the present study, only the two outside trays were filled with round metal pegs while the middle trays were left empty (they are used in another type of test not incorporated into this study). For the test, the subject was given a specific amount of time (30 seconds, unknown to subject) to place as many pegs into the appropriate column of the board as possible. The number of pegs placed in the board was recorded as the score.

The PPB was placed right to the edge of the table in front of the subject (peg trays closest to experimenter). It was explained that the object of this test was to fill the columns of this pegboard from top to bottom as quickly as possible for a short period of time using only one hand at a time. It was also pointed out that since the pegs were

round, they have a tendency to roll away. Subjects were told that if a peg rolled away during the test, they were to ignore it and reach for another peg from the tray. When subjects used their right hand for the test, they were to grab one peg from the right peg tray and place it in the top hole of the right column. The left peg tray and left column were used when subjects used their left hand. A trial in which both hands were used to fill the respective columns in the board was run after each hand was tested. Subjects were to simultaneously grab pegs from each tray and place them in the top hole of the respective columns. A practice trial was allowed for each trial in which the subject filled the first five holes of the column. Each trial lasted 30 seconds after which the number of pegs placed in the board was recorded as the score. Subjects would have their score reduced if they grabbed more than one peg from the tray or used their other hand to insert pegs into the column.

B.3 Parent Rating Scales:

B.3.1 Conners' Parent Rating Scale (Revised)

The Conners' Parent Rating Scale (Revised) (CPRS-R; Goyette, et al., 1978) is a questionnaire that has parents rate their child's behavior on 48 items. Each item is scored on a three-point scale ranging from 'not at all'(0, absent), to 'just a little'(1), 'pretty much'(2), and 'very

much'(3). Dimensions measured by the CPRS-R include conduct, psychosomatic, impulsive-hyperactive, anxiety, and learning problems. Also, a hyperkinesis index is calculated through scoring the CPRS-R.

B.3.2 Child Behavior Checklist

The Child Behavior Checklist (CBCL; Achenbach, 1991) is a comprehensive behavior rating scale that assesses both behavior problems and competency of the child in various social situations. The child is rated on 138 items using a three-step rating scale. This scale ranges from 'not true'(0), to 'somewhat/sometimes true'(1), and 'very true/ often true'(3). There are two parts to the CBCL. The first section of the CBCL assesses the competency of the child in various situations. Activity, social, and school competency are calculated by scoring this section of the test. A total social competency index is determined by summing the scores on these three indices. The second part derives eight indices of behavior. These indices are: withdrawn, somatic complaints, anxious-depressed, social problems, thought problems, attention problems, delinquent, and aggressive behavior problems. Also, there are subscales that are calculated by summing selected factors: the internalizing index is the sum of withdrawn, somatic, and anxious-depressed indices; the externalizing

index is the sum of delinquent and aggressive behavior indices, and a total index that is the sum of all indices.

B.4 Procedure

An information sheet about the study was given to the parents to read before consent was obtained (see appendix B). The motor tests examined in this study were part of a larger test battery that took approximately one 90 minute test session to complete. Within this battery, the motor tests followed the administration of either the Conners' Continuous Performance Test (Conners, 1992; Multi-Health Systems, 65 Overlea Blvd., Suite 210, Toronto, ON, M4H 1P1) or the Vigilance Task of the Gordon Diagnostic System (Gordon, 1987; Gordon Systems Inc., DeWitt, New York, 13214). The order of tests in the motor block of the testing procedure is as follows: DYN, FTT, GPT, PPB. While subjects were tested, parents filled out behavior rating questionnaires. After testing procedure was complete, the parent, subject, and researcher discussed any concerns or questions that may have arisen from the procedures performed with the subject or questionnaires given to the parent.

C Results

Data were analyzed by different means according to whether variables were normally or non-normally distributed. For handedness and behavioral rating scales, Mann-Whitney U analyses were performed as these variables were non-normally distributed. Age was compared between groups using a simple analysis of variance (ANOVA). Analysis was also performed on subgroups of subjects (unless otherwise indicated). Groups were split into young (6-8 years) and old (9-14 years) age subgroups due to test administration procedures (see previous section). Motor performance on the four tests was compared between groups with multivariate analyses of covariance (MANCOVAs), while performance asymmetry measures were compared using analyses of covariance (ANCOVAs). Finally, prevalence and consistency of asymmetry were compared between groups using chi-square (χ^2) analysis or the Fisher Exact P statistic when all assumptions of χ^2 analysis could not be met (Siegel, 1956).

C.1 Subjects

Examination of the histograms of scores on handedness and behavioral measures found that the data were *not normally distributed.* The scoring procedures on the CPRS-R and CBCL (normal scored at zero with no negative numbers attainable) and the distribution of handedness in the general population (right>left) resulted in a

truncation in the normal distribution for all variables. Because of the non-normal distribution, non-parametric statistics were used to analyze the difference in mean measures between ADHD and control groups. For the CPRS-R raw scores were standardized to T-scores using age-appropriate published norms (Goyette et al., 1978). Scores on the CBCL had T-scores already calculated by the scoring software. Imposed T-score cutoffs of 50 on behavior factors and of 55 on the competence factors are used by the scoring program to prevent 'over interpretation of normal scores' on the CBCL. No imposed cutoffs were used in the scoring of the CPRS-R. Since there were many significance tests being run, the α level of .05 was adjusted with the Bonferroni procedure ($\alpha^*=\alpha/k$; where k= number of tests being run) to correct for the cumulative experimental error that is encountered by running many statistical comparisons (Krauth, 1988). For the behavioural measures, the adjusted significance level used was: $\alpha^*=$ .05/17= .0029.

A between group ANOVA found no significant differences in age, while Mann-Whitney U analysis found no significant differences in handedness between subject groups. Results from parental ratings of behavior are presented in Table 3 and graphically in Figures 7 to 9. The ADHD subjects had significantly higher T-scores on the CPRS-R

Table 3: Results from behavior rating scales. Mean T-score and standard error (SEM) are presented for each measure on the Conners' Parent Rating Scale (Revised) (CPRS-R) and the Child Behavior Checklist (CBCL).

Index Measure	CONTROL		ADHD	
	MEAN	SEM	MEAN	SEM
CPRS-R Behavior Scales				
Learning Problem	52.08	2.81	77.23*	2.33
Psychosomatic	52.61	3.04	62.07	4.28
Impulsive-Hyperactive	47.95	2.50	70.91*	1.87
Anxiety	53.64	2.19	60.70	3.56
Conduct Problem	47.58	2.44	62.11†	3.37
Hyperkinesis Index	48.44	2.24	73.99*	2.10
CBCL Behavior Scales				
Withdrawn	53.25	1.05	59.54	2.11
Somatic Complaints	56.42	1.37	61.58	2.10
Anxious-Depressed	57.25	1.82	64.58	2.21
CBCL Internalizing	53.67	2.35	63.79	2.40
Delinquent Behavior	53.46	1.12	58.96	1.72
Aggressive Behavior	54.42	1.36	63.37‡	2.25
CBCL Externalizing	50.08	2.17	61.58‡	2.21
Social Problems	55.00	1.25	66.79*	1.95
Thought Problems	55.96	1.48	62.67	2.22
Attention Problems	56.38	2.04	74.00*	2.06
CBCL Total Score	52.92	2.38	67.25*	1.85
CBCL Competency Scales				
Activity Competency	49.30	1.19	46.21	2.20
Social Competency	46.33	1.75	40.61	1.27
School Competency	41.14	2.04	36.75	1.78
Total Competency Score	47.05	2.10	39.92	1.70

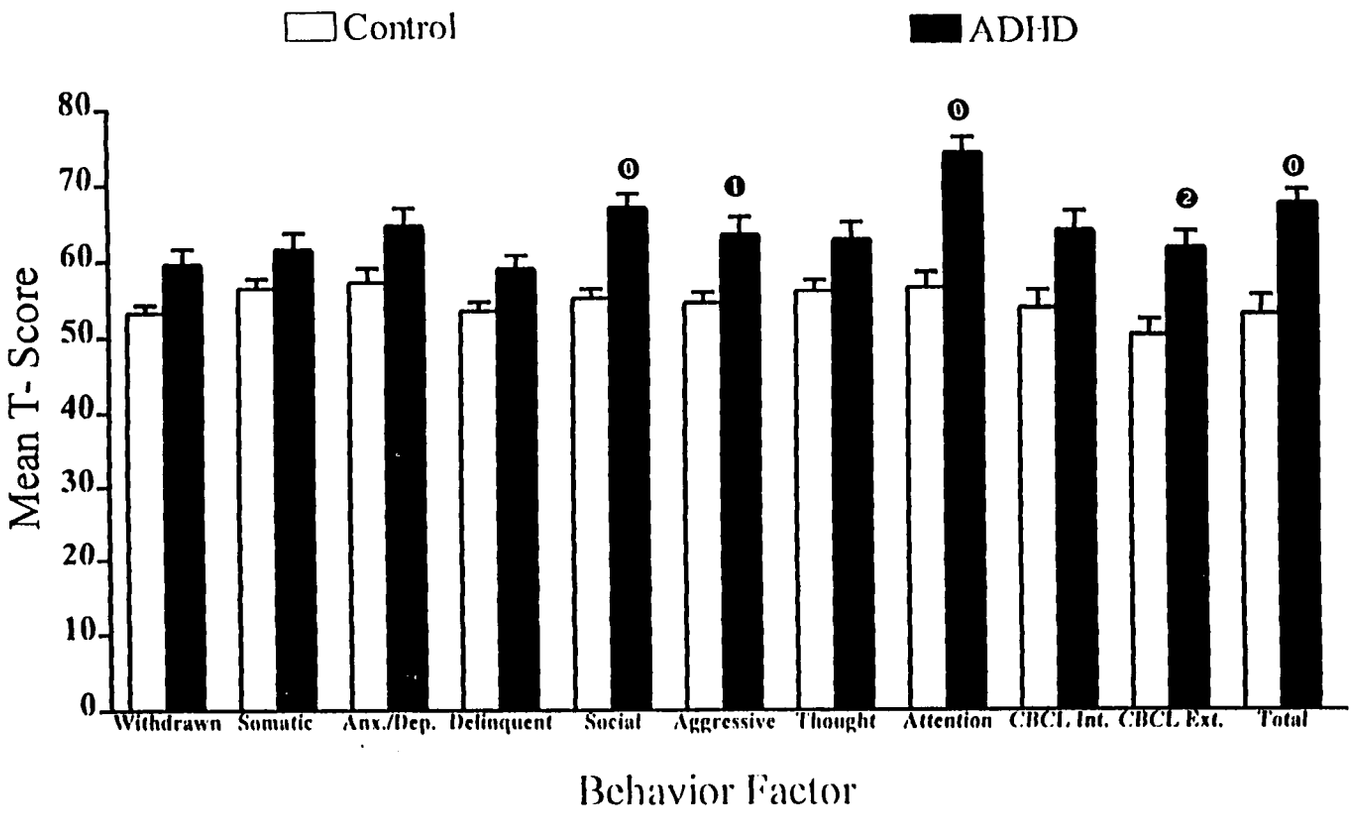
* indicates significantly different ($p<.0001$) from control subjects.

† indicates significantly different ($p<.0005$) from control subjects.

‡ indicates significantly different ($p<.001$) from control subjects.

Figure 7: Bar chart comparing ADHD and control subjects on the Child Behavior Checklist behavior factors. ❶ significantly different from control group ($p<.0001$), ❶ significantly different from control group ($p<.0005$), ❷ significantly different from control group ($p<.001$). Abbreviations are as follows: ADHD: attention deficit hyperactivity disorder, CBCL Int.: Child Behavior Checklist Internalizing Scale, CBCL Ext.: Child Behavior Checklist Externalizing Scale, Anx./Dep.: Anxious/Depressed behavior factor.

Mean Parental Behavioral Ratings of ADHD and Control Subjects on Behavior Factors of the Child Behavior Checklist



Mean Parental Behaviour Ratings of ADHD and Control Subjects on Competency Factors of the Child Behavior Checklist

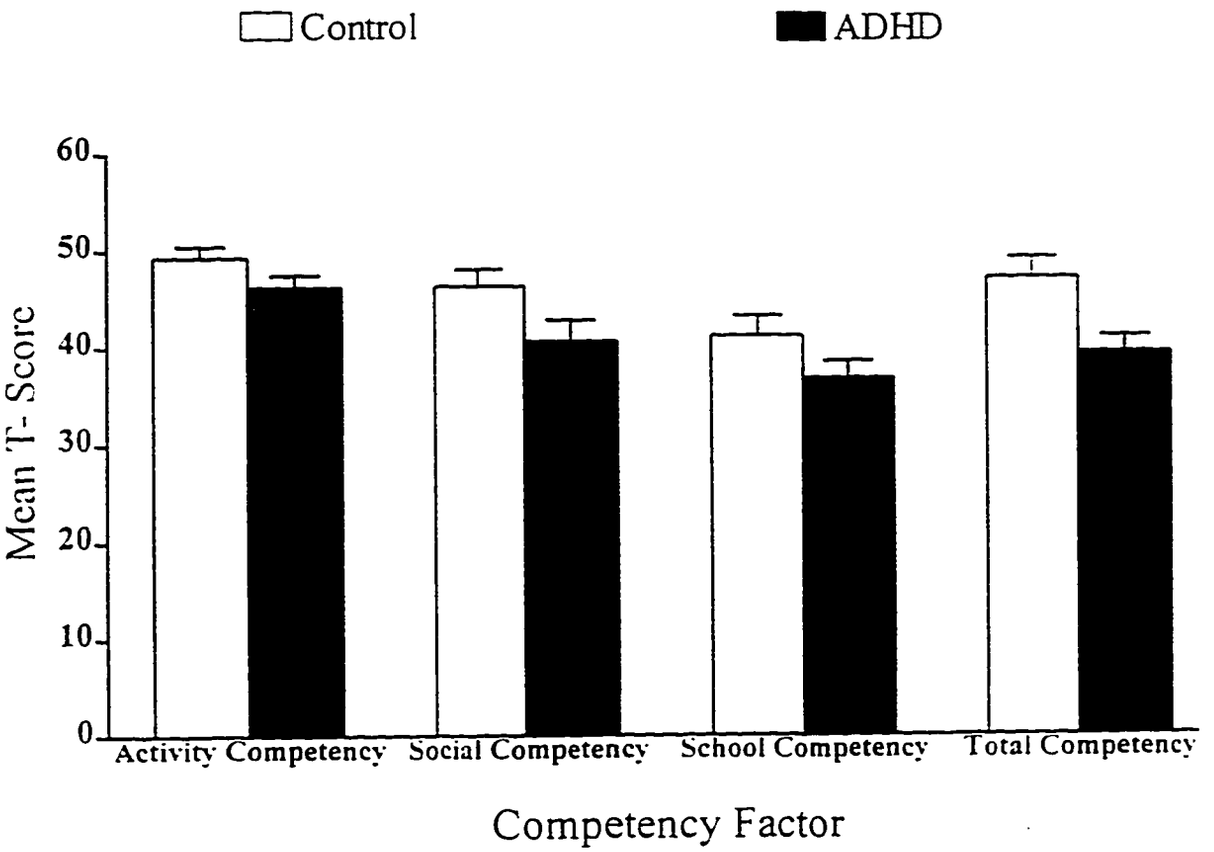
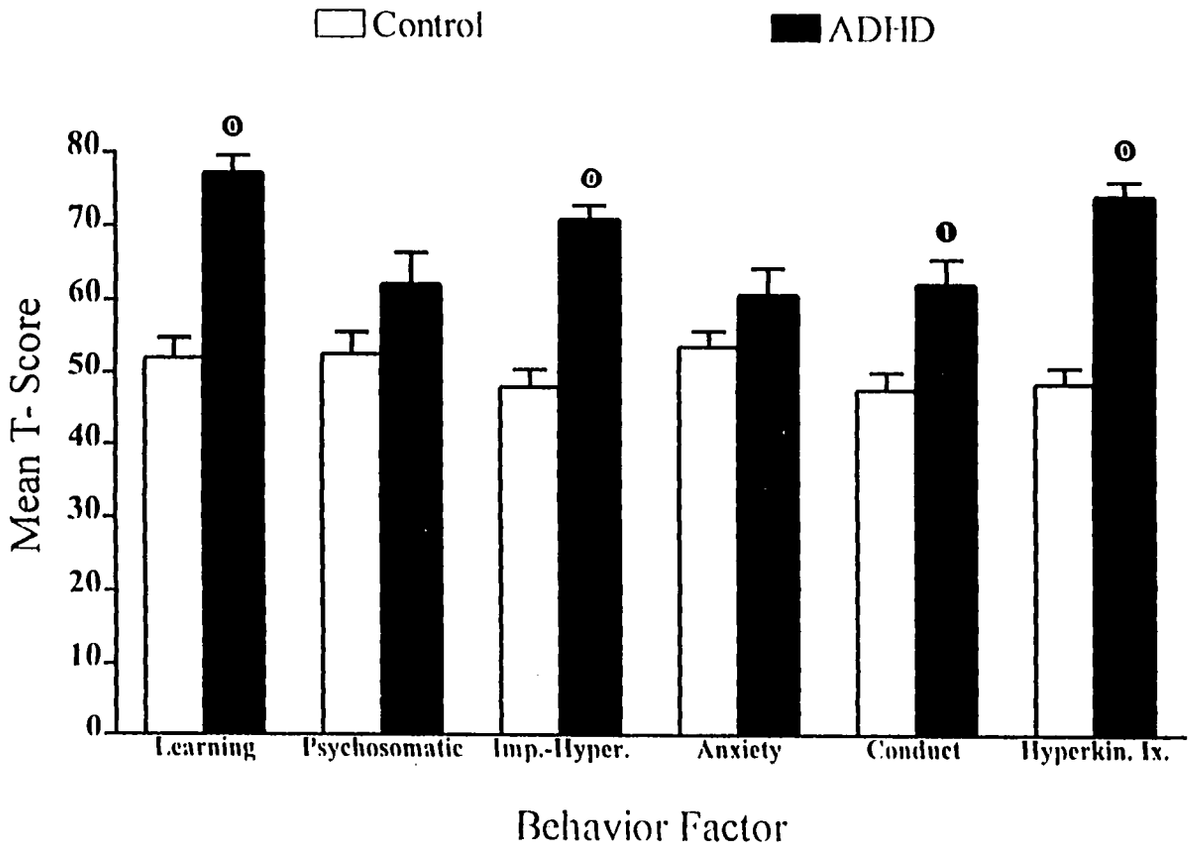


Figure 8: Bar charts comparing ADHD and control subjects on parental ratings of behavior competency factor ratings from the Child Behavior Checklist. Abbreviations are as follows: ADHD: attention deficit hyperactivity disorder

Figure 9: Bar chart comparing ADHD and control subjects on the Conners Parent Rating Scale (Revised). ❶ significantly different from control group ($p<.0001$), ❶ significantly different from control group ($p<.0005$). Abbreviations are as follows: ADHD: attention deficit hyperactivity disorder, Imp.-Hyper.: Impulsive Hyperactive behavior factor, Hyperkin. Ix.: Hyperkinesis Index.

Mean Parental Behavioral Ratings of ADHD and Control Subjects on Behavior Factors of the Conners' Parent Rating Scale (Revised)



hyperkinesis index (U= 21.5, z= -5.505, p<.0001) and the CBCL attention scale (U= 62.5, z= -4.700, p<.0001) versus controls. Also, as can be shown in Figure 7C, ADHD subjects significantly had higher T-scores on the impulsive/hyperactive (U= 52.5, z= -4.877, p< .0001), learning problems (U= 51.5, z= -4.900, p<.0001), and conduct problems (U= 110.0, z= -3.686, p<.0005) factors of the CPRS-R. Figure 7 shows that ADHD subjects had significantly higher scores on the social (U=92.0, z= -4.077, p<.0001) and aggressive (U= 128.0, z= 3.346, p<.001) behavior variables on the CBCL. Also, ADHD subjects had significantly higher scores on the externalizing (U= 130.0, z= -.326, p<.001) and total (U= 96.5, z= -2.43, p<.0001) scores of the CBCL (Figure 7). Parental behavior ratings of psychosomatic complaints and anxiety on the CPRS-R (Figure 9) and thought, somatic, delinquent, withdrawn, anxious-depressed and internalizing scales on the CBCL (Figure 7) did not significantly differ between subjects. None of the social competency scores of the CBCL significantly differed between subjects (Figure 8).

Some neuropsychological testing procedures differ depending upon the age of the subject as described in the motor test administration procedures. As a result, subjects were split into young (6-8 years) and old (9-14 years) subgroups for data analysis. No significant

differences were found between ADHD and normal control groups when young and old subgroups were analyzed for differences in age or handedness. Analysis was not performed on behavior rating scale variables for separate age subgroups.

C.2 Motor Performance Measures

MANCOVAs, controlling for age, compared ADHD and control groups' performance on the PPB, FTT, DYN, and GPT (young and old subgroups) for preferred and non-preferred hands (including both hands on the PPB).

Multivariate analysis of motor performance data showed a significant effect for the PPB ($F(3, 43) = 3.448$, $p = .025$). Following the MANCOVA, individual variable differences were examined using Roy-Bose simultaneous 95% confidence intervals. Simultaneous confidence intervals maintain the type I error rate at the .05 level for all variables tested (Morrison, 1976). The only variable determined to be significantly different between subjects on the PPB was performance with the preferred hand (Table 4 and Figure 10). MANCOVA testing on the remaining three motor tests used in this study revealed no significant effects. Table 4 and Figures 11-14 show

Table 4: Results from motor tests. Mean and standard error (SEM) are presented for preferred (Pr) and non-preferred (NP) hands on the hand dynamometer (DYN), finger tapping test (FTT), grooved pegboard test (GPT, GPT5), and Purdue Pegboard (PPB).

GPT5 - grooved pegboard test, all five rows
* indicates significantly different from Control (all) group (Re: 95% Roy-Bose simultaneous confidence interval [Morrison, 1976])
† used electric finger tapping test
‡ only filled first two rows of grooved pegboard

Test	Hand	*Control all N=24*		*ADHD all N=24*		*Control young N=9*		*ADHD young N=8*		*Control old N=15*		*ADHD old N=16*	
		Mean	*SEM*	*Mean*	*SEM*	*Mean*	*SEM*	*Mean*	*SEM*	*Mean*	*SEM*	*Mean*	*SEM*
DYN	**Pr**	17.28	1.43	16.10	1.10	11.11	1.26	11.75	1.26	20.98	1.49	18.28	1.21
	NP	16.48	1.24	15.85	1.19	10.67	.98	11.00	1.26	19.97	1.19	18.28	1.31
FTT	**Pr**	42.03	1.02	39.99	1.19	40.67†	.83	39.65†	1.32	42.85	1.55	40.16	1.68
	NP	37.63	.73	36.47	.89	36.78†	.74	36.38†	1.49	38.13	1.09	36.53	1.15
GPT	**Pr**	-	-	-	-	30.11‡	1.70	29.88‡	1.96	59.13	1.60	63.44	2.33
	NP	-	-	-	-	35.56‡	2.24	35.88‡	1.49	77.00	10.42	73.06	4.37
GPT5	**Pr**	66.29	2.46	69.13	2.80	78.22	3.22	80.50	5.12	59.13	1.60	63.44	2.33
	NP	82.71	7.03	82.00	4.20	92.22	6.63	99.88	4.83	77.00	10.42	73.06	4.37
PPB	**Pr**	13.83	.43	12.42*	.50	12.44	.53	10.13	.40	14.67	.51	13.56	.53
	NP	12.42	.49	11.63	.50	10.89	.73	10.00	.53	13.33	.53	12.44	.61
	Both	10.71	.36	9.88	.44	10.33	.60	8.00	.65	10.93	.45	10.81	.41

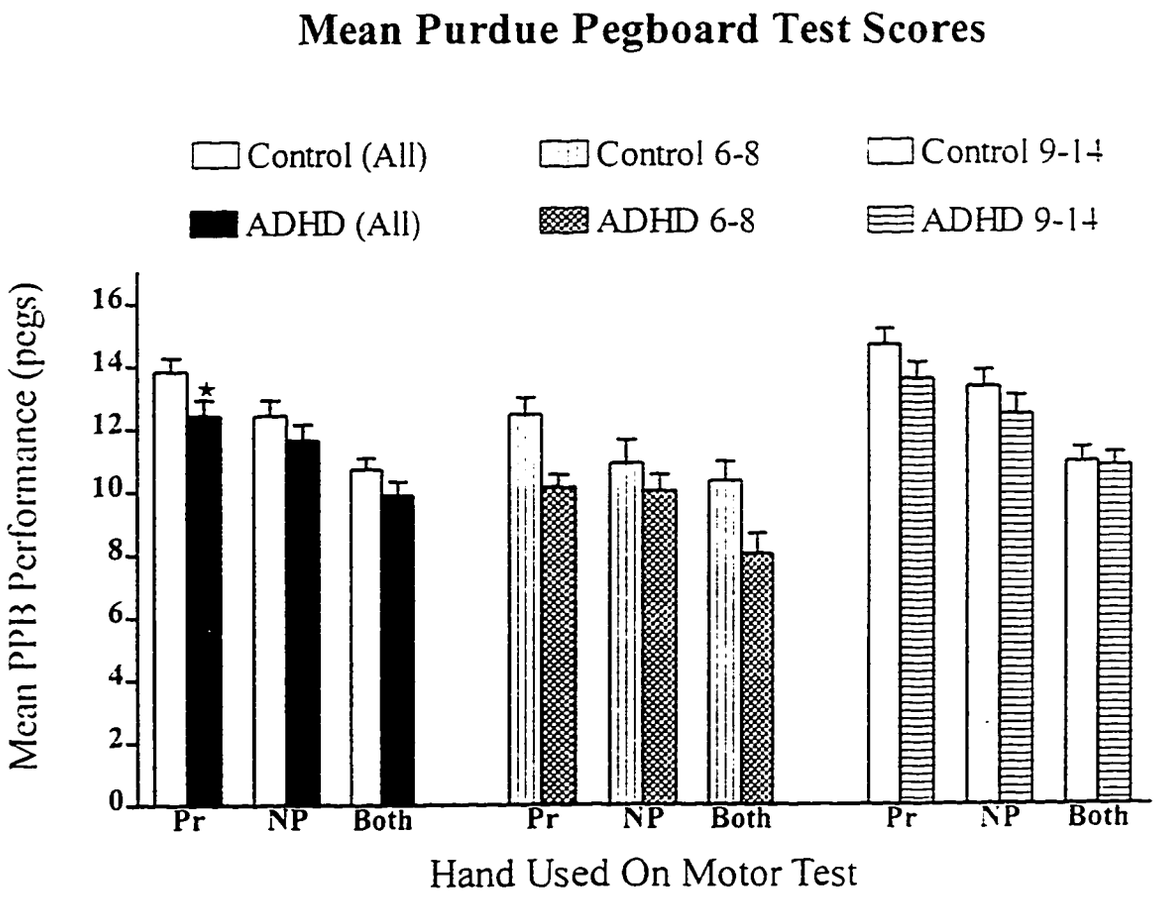


FIGURE 10: Bar chart comparing motor performance scores between ADHD and control subject subgroups and together as a whole for the PPB. Significant difference from the control group is indicated with ★ (Re: 95% Roy-Bose simultaneous confidence interval). Abbreviations are as follows: ADHD: attention deficit hyperactivity disorder, Pr: preferred hand, NP: non-preferred hand, PPB: Purdue pegboard.

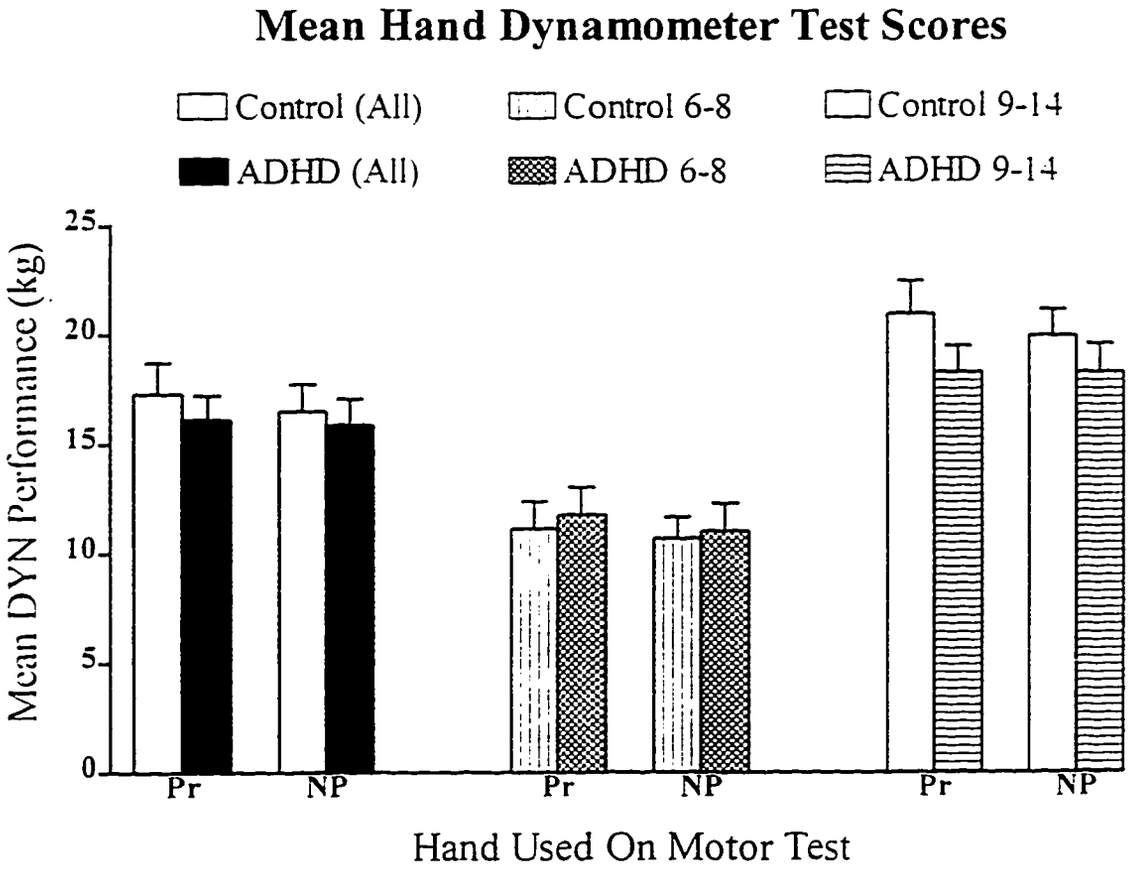


Figure1 1: Bar chart comparing motor performance scores between ADHD and control subject subgroups and together as a whole for the DYN. Abbreviations are as follows: ADHD: attention deficit hyperactivity disorder, Pr: preferred hand, NP: non-preferred hand, DYN: hand dynamometer test.

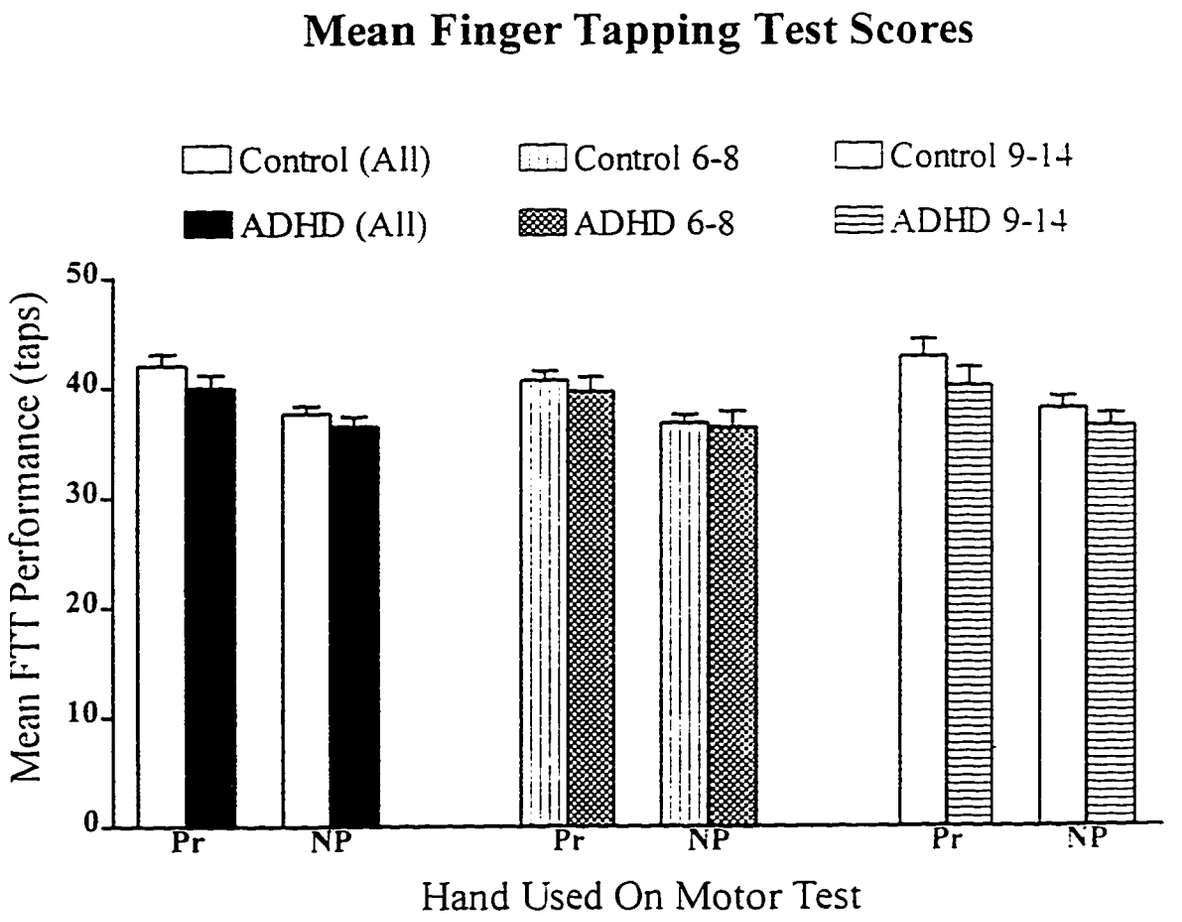


FIGURE 12: Bar chart comparing motor performance scores between ADHD and control subject subgroups and together as a whole for the FTT. The younger subgroup (6-8 years) used an electric FTT whils older subjects used the manual FTT. Abbreviations are as follows: ADHD: attention deficit hyperactivity disorder. Pr: preferred hand, NP: non-preferred hand, FTT: finger tapping test.

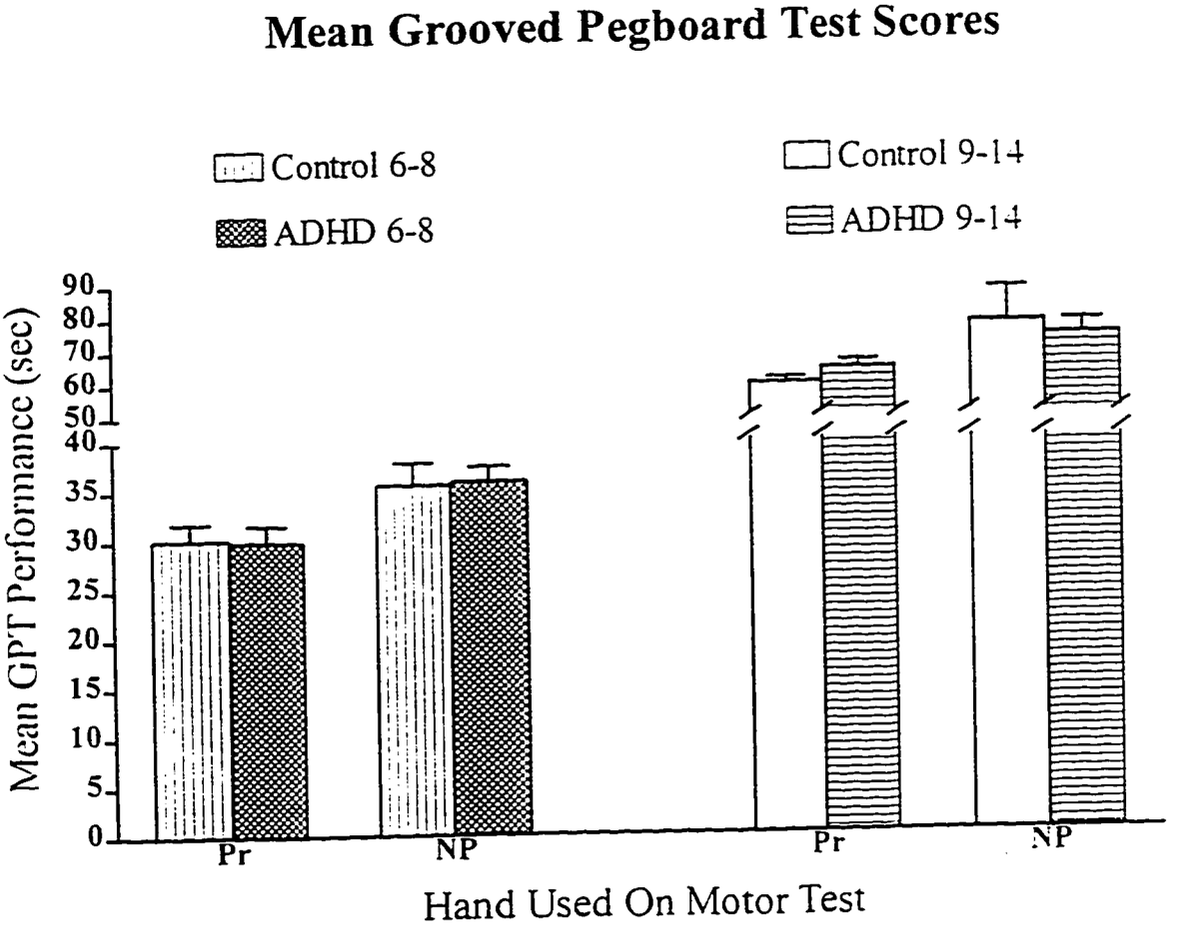


FIGURE 13: Bar chart comparing motor performance scores between ADHD and control subject subgroups for the GPT. Standard administration of the GPT requires younger subjects to fill out the first two rows of the pegboard while older subjects fill the entire board. Abbreviations are as follows: ADHD: attention deficit hyperactivity disorder, Pr: preferred hand, NP: non-preferred hand. GPT: grooved pegboard test.

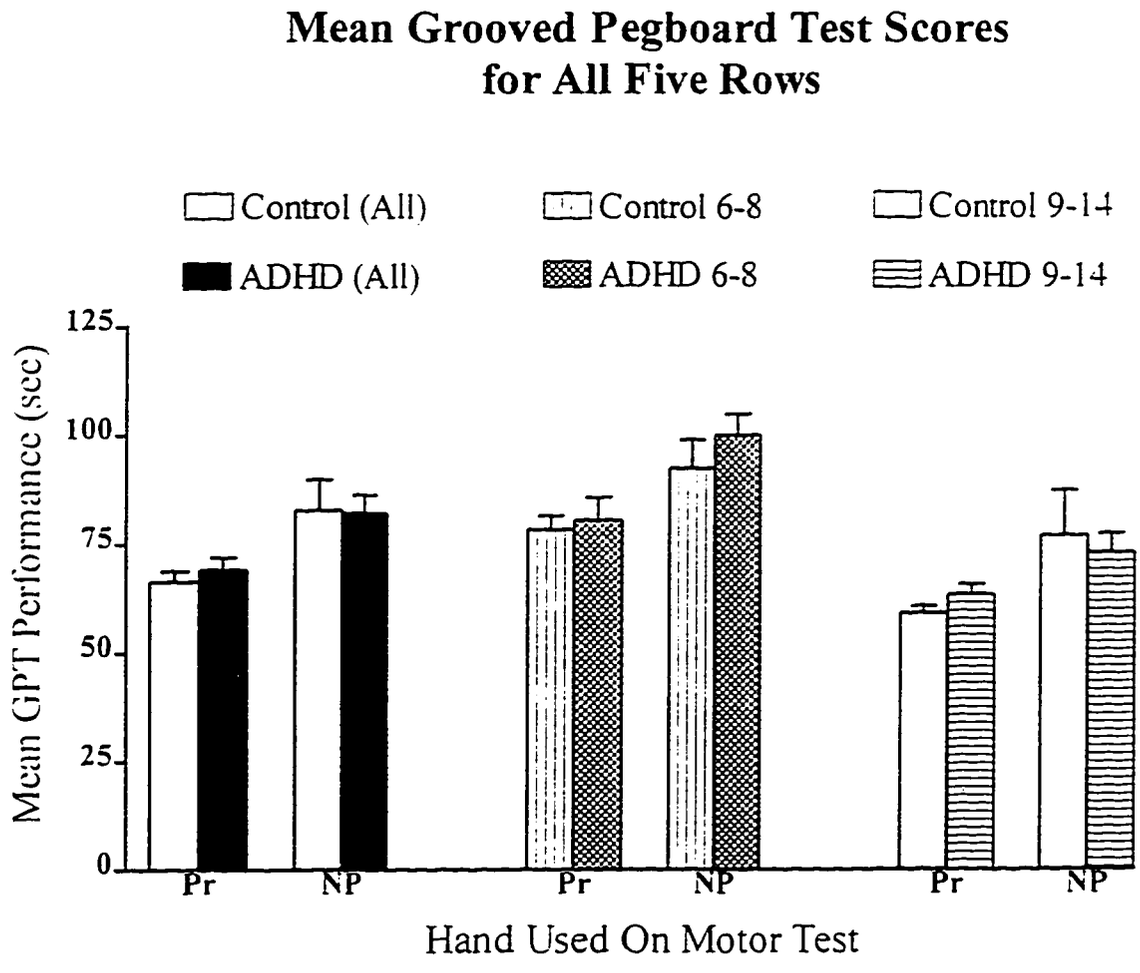


FIGURE 14: Bar chart comparing motor performance scores between ADHD and control subject subgroups and together as a whole on the GPT 5. Abbreviations are as follows: ADHD: attention deficit hyperactivity disorder, Pr: preferred hand, NP: non-preferred hand. GPT 5: grooved pegboard test for all five rows.

that there were no other significant differences found between groups on any of the remaining motor measures.

When the scores were analyzed by age subgroups, the significant effect on the PPB followed to the younger ($F(3,12) = 3.968$, $p = .035$) but not older ($p = .246$) subgroup of subjects. Examination of the 95% Roy-Bose confidence intervals did not reveal any significant differences in individual variables for young or old subgroups. Figures 11-14 show that there were no significant differences on any other motor performance measures for the age subgroups.

C.3 Performance Asymmetry Scores

The four different methods of calculating performance asymmetry described in the Method section were performed in order to make results comparable with those of other studies (Dodrill, 1978, Andrew, 1981; Bornstein, 1986a, 1986b; Carlier et al., 1994; Panich et al., 1994; Seidman et al., 1995; Massman and Doody, 1996). Individual measures of performance asymmetry were compared with ANCOVA controlling for age. These values were linearly dependent on each other and were unsuitable for multivariate analysis. The Bonferroni procedure was used to adjust the α level for these univariate

significance tests (Krauth, 1988). The adjusted significance level for comparing the intermanual difference scores was: $\alpha^* = .05/20 = .0025$.

Table 5 and Figures 15-34 show that there were no significant differences between groups on any measures of performance asymmetry for all motor tests. The same results were found even when lateralization scores were analyzed by subgroup.

C.4 Prevalence and Consistency of Motor Asymmetries

The percentage of subjects showing an asymmetrical motor pattern was calculated. The criteria for asymmetrical motor performance were based on a study by Massman and Doody (1996) who examined performance asymmetry on the FTT in patients with Alzheimer Disease. These criteria set the normal range of performance asymmetry at greater than 0% and less than 20%. Subjects performing outside this range, having either reversed asymmetry (0% or less) or an exaggerated preferred hand asymmetry (20% or greater), were classified as asymmetrical performers. While these criteria have previously been used to hypothesize neural dysfunction on two of the motor tests used in this study (FTT, DYN; Golden, 1981), these criteria were elaborated to classify performance on all motor tests used in this project. ADHD and control groups were compared on each motor test

Table 5: Mean performance asymmetry results for the hand dynamometer (DYN), finger tapping test (FTT), grooved pegboard test (GPT, GPT5), and Purdue Pegboard (PPB). Asymmetry scores are presented using the laterality quotient (LQ), dominance ratio (DR), non- preferred - preferred ratio (NP/Pr), and preferred minus non-preferred (Pr-NP) formulae.

Perf. Asym. Form.- Performance asymmetry formula
GPT5- grooved pegboard test, all five rows
† Pr and NP scores were interchanged in calculating performance asymmetry for the GPT and GPT5 (Bornstien, 1986a)

Test	Perf. Asym. Form.	*Control (all) N=24*		*ADHD (all) N=24*		*Control (young) N=9*		*ADHD (young) N=8*		*Control (old) N=15*		*ADHD (old) N=16*	
		Mean	*SEM*	*Mean*	*SEM*	*Mean*	*SEM*	*Mean*	*SEM*	*Mean*	*SEM*	*Mean*	*SEM*
DYN	LQ	1.63	1.13	1.28	1.26	.95	1.94	3.47	1.84	2.04	1.42	.19	1.61
	DR	2.64	2.26	1.87	2.35	1.26	4.09	6.28	3.36	3.47	2.75	-.34	3.01
	NP/Pr	.97	.02	.98	.02	.99	.04	.94	.03	.97	.03	1.00	.03
	Pr-NP	.80	.41	.25	.40	.44	.38	.75	.41	1.02	.61	.00	.57
FTT	LQ	5.40	.74	4.41	1.00	5.01	.92	4.42	1.84	5.64	1.06	4.40	1.24
	DR	10.04	1.32	8.03	1.86	9.43	1.69	8.04	3.43	10.41	1.89	8.03	2.28
	NP/Pr	.90	.01	.92	.02	.91	.02	.92	.03	.90	.02	.92	.02
	Pr-NP	4.41	.63	3.51	.80	3.89	.73	3.28	1.38	4.72	.92	3.63	1.01
GPT[1]	LQ	9.01	2.34	7.48	1.42	8.12	2.60	9.55	2.95	9.54	3.47	6.45	1.56
	DR	14.89	3.35	13.19	2.40	14.15	4.55	16.51	4.93	15.34	4.73	11.53	2.65
	NP/Pr	.85	.03	.87	.02	.86	.05	.83	.05	.85	.05	.88	.03
	Pr-NP	-	-	-	-	5.44	1.88	6.00	1.87	17.87	9.82	9.63	2.81
GPT5[1]	LQ	8.82	2.24	7.95	1.52	7.62	1.75	10.96	3.25	9.54	3.47	6.45	1.56
	DR	14.75	3.11	13.91	2.53	13.77	2.94	18.66	5.32	15.34	4.73	11.53	2.65
	NP/Pr	.85	.03	.86	.03	.86	.03	.81	.05	.85	.05	.88	.03
	Pr-NP	16.42	6.24	12.88	2.72	14.00	4.03	19.38	5.50	17.87	9.82	9.63	2.81
PPB	LQ	5.81	1.51	3.41	2.37	7.27	3.06	.79	3.47	4.94	1.63	4.72	3.13
	DR	10.12	2.63	4.41	4.19	12.34	5.35	-.01	6.61	8.79	2.84	6.62	5.41
	NP/Pr	.90	.03	.96	.04	.88	.05	1.00	.07	.91	.03	.93	.05
	Pr-NP	1.42	.36	.79	.52	1.56	.67	.13	.72	1.33	.67	1.13	.69

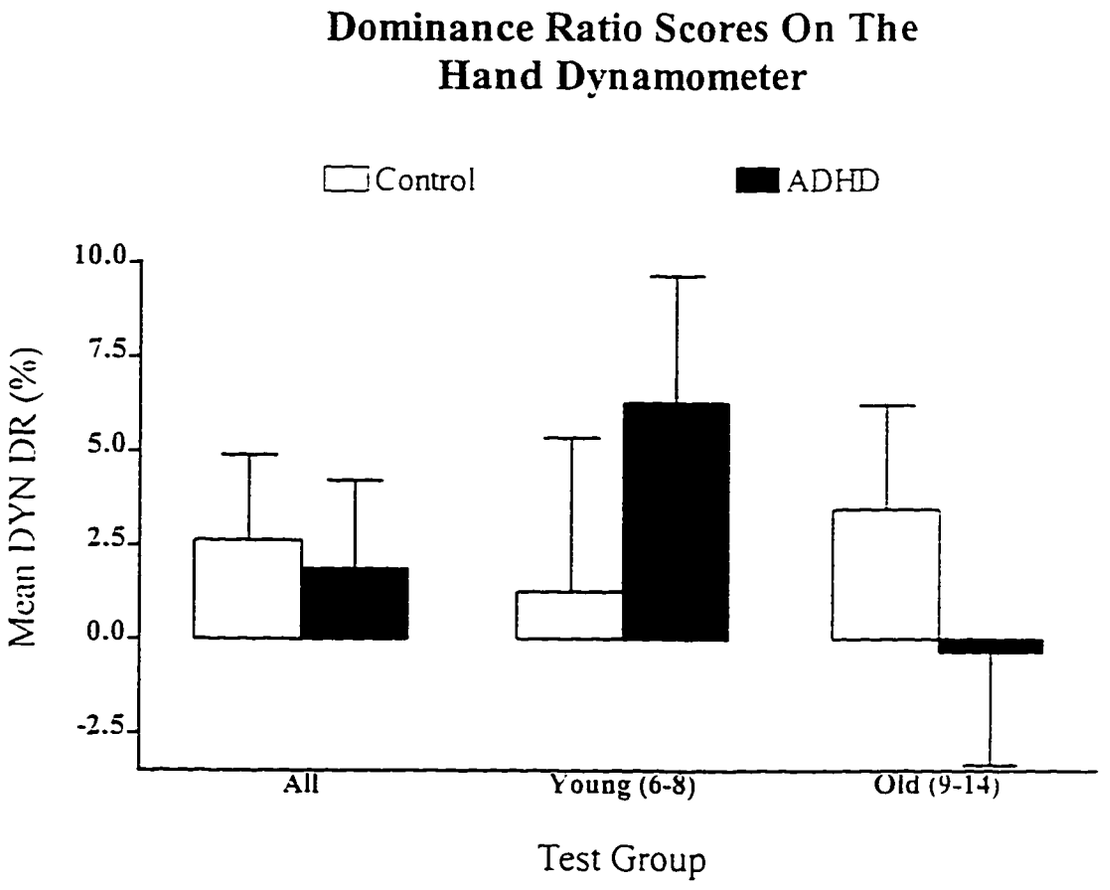


Figure 15: Bar chart comparing ADHD and control subjects on the Dominance Ratio measure of performance asymmetry ([{Pr-NP}/Pr] X 100) on the DYN. Scores are presented for individual subgroups and for total ADHD and control groups. Abbreviations are as follows: ADHD: attention deficit hyperactivity disorder. Pr: preferred hand. NP: non-preferred hand. DYN: hand dynamometer test. DR: dominance ratio.

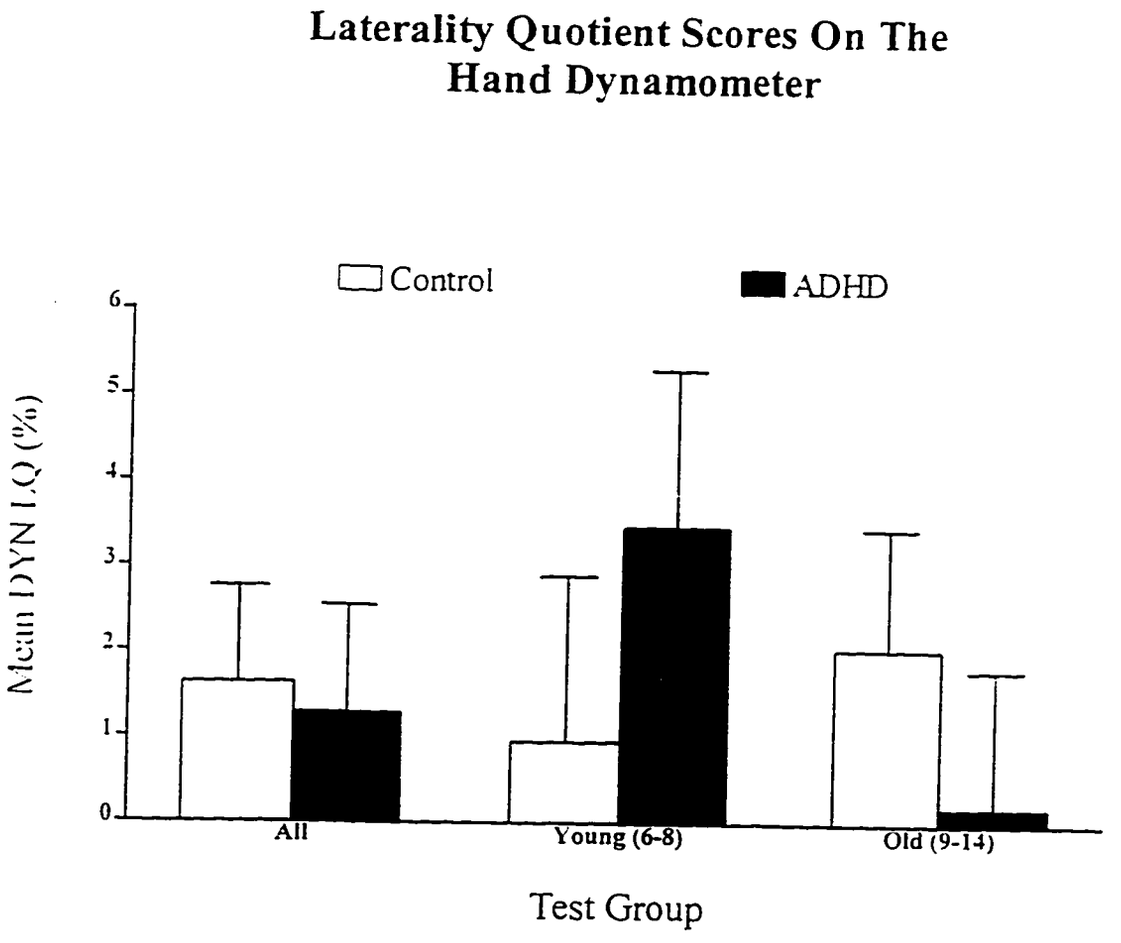


Figure 16: Bar charts comparing ADHD and control subjects on the Laterality Quotient measure of performance asymmetry ([{Pr-NP}/{Pr+NP}] X 100) on the DYN. Scores are presented for individual subgroups and for total ADHD and control groups. Abbreviations are as follows: ADHD: attention deficit hyperactivity disorder, Pr: preferred hand, NP: non-preferred hand, DYN: hand dynamometer test, LQ: laterality quotient.

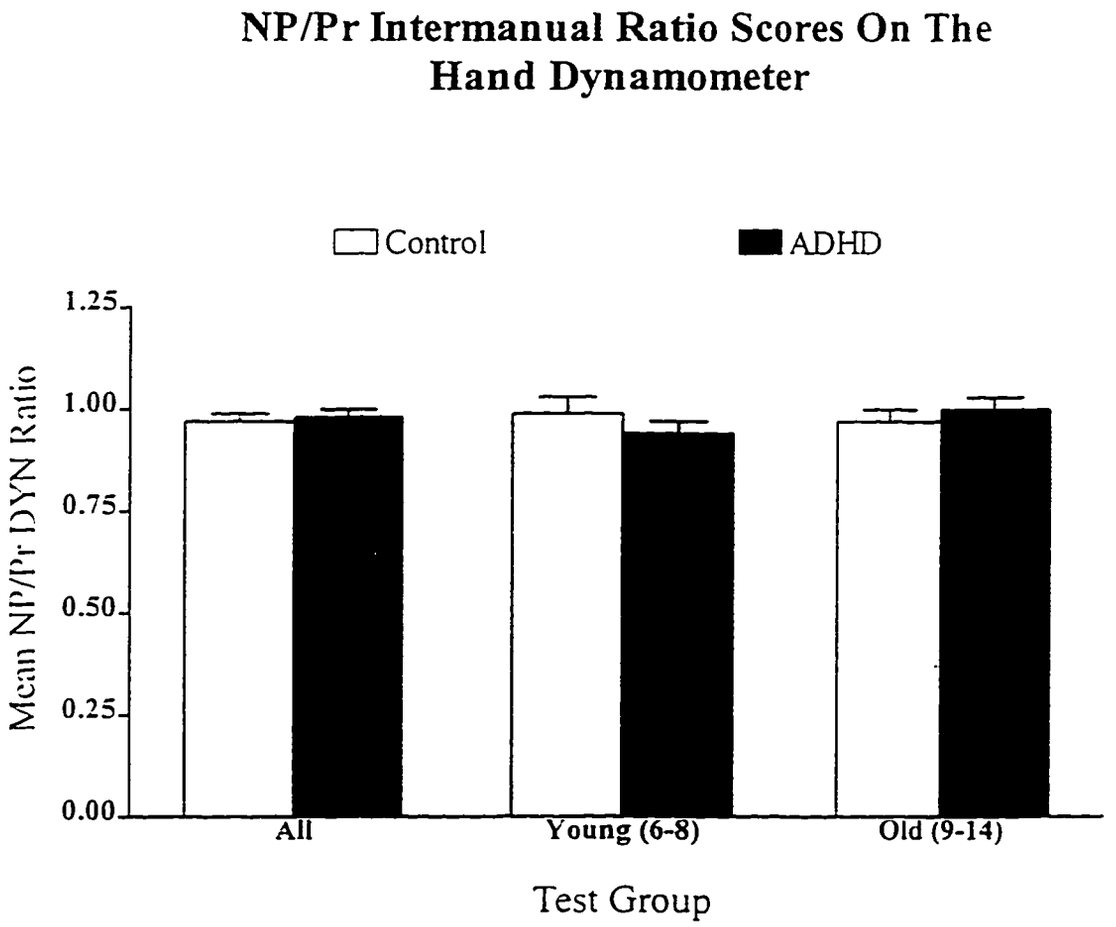


Figure 17: Bar chart comparing ADHD and control subjects on the NP/Pr measure of performance asymmetry on the DYN. Scores are presented for individual subgroups and for total ADHD and control groups. Abbreviations are as follows: ADHD: attention deficit hyperactivity disorder, Pr: preferred hand, NP: non-preferred hand, DYN: hand dynamometer test.

Pr-NP Scores On The Hand Dynamometer

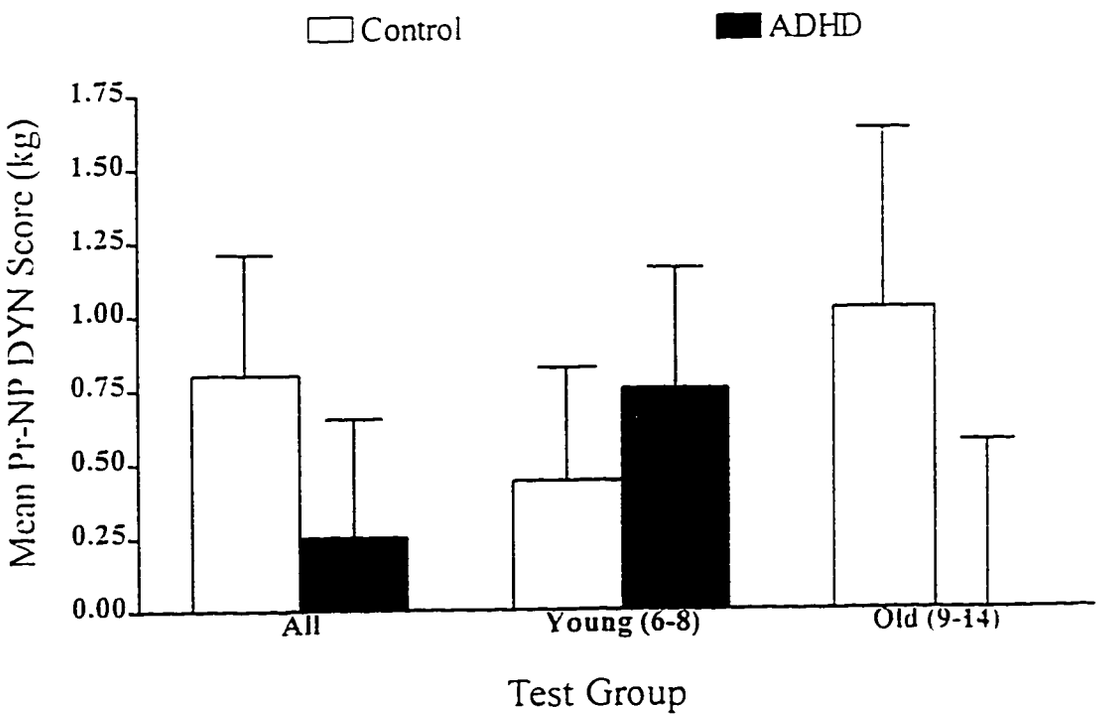


Figure 18: Bar chart comparing ADHD and control subjects on th Pr-NP measure of performance asymmetry on the DYN. Scores are presented for individual subgroups and for total ADHD and control groups. Abbreviations are as follows: ADHD: attention deficit hyperactivity disorder, Pr: preferred hand, NP: non-preferred hand. DYN: hand dynamometer test.

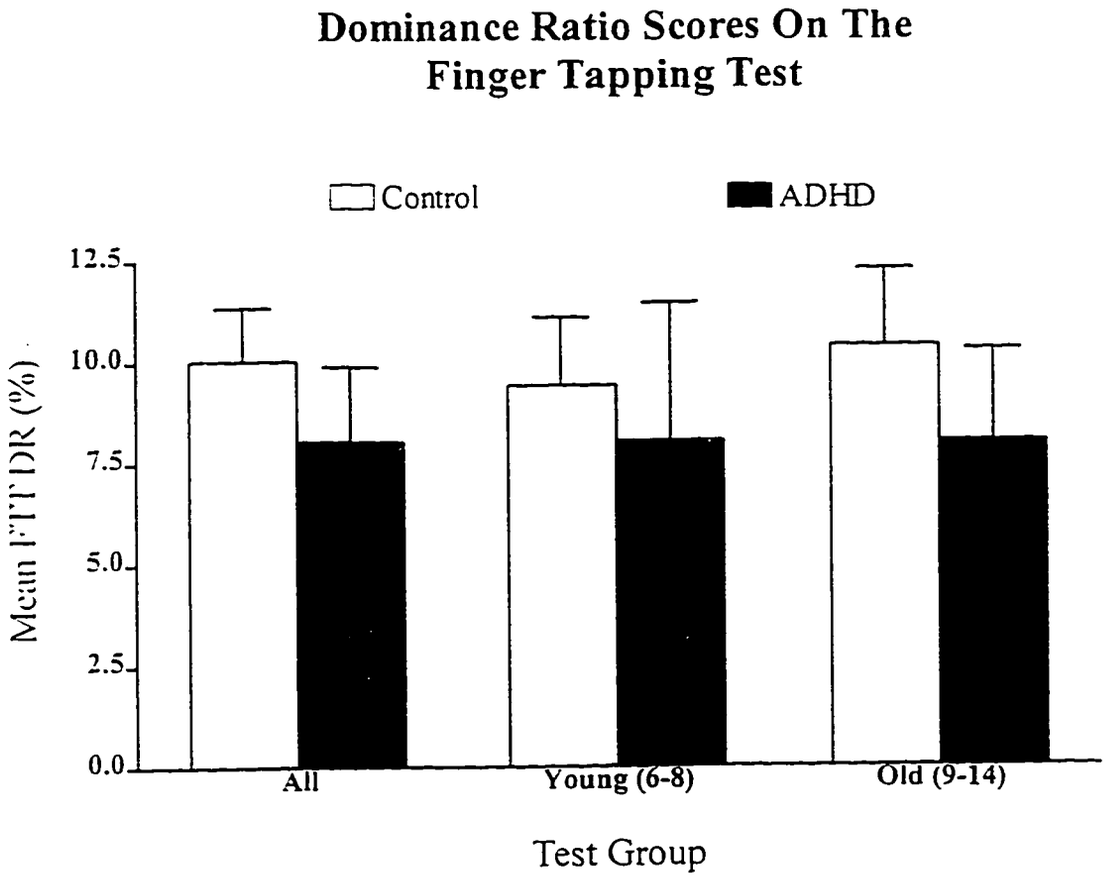


Figure 19: Bar chart comparing ADHD and control subjects on the Dominance Ratio measure of performance asymmetry ([{Pr-NP}/Pr] X 100) on the FTT. Scores are presented for individual age subgroups and for total ADHD and control groups. Abbreviations are as follows: ADHD: attention deficit hyperactivity disorder, Pr: preferred hand, NP: non-preferred hand, FTT: finger tapping test, DR: dominance ratio.

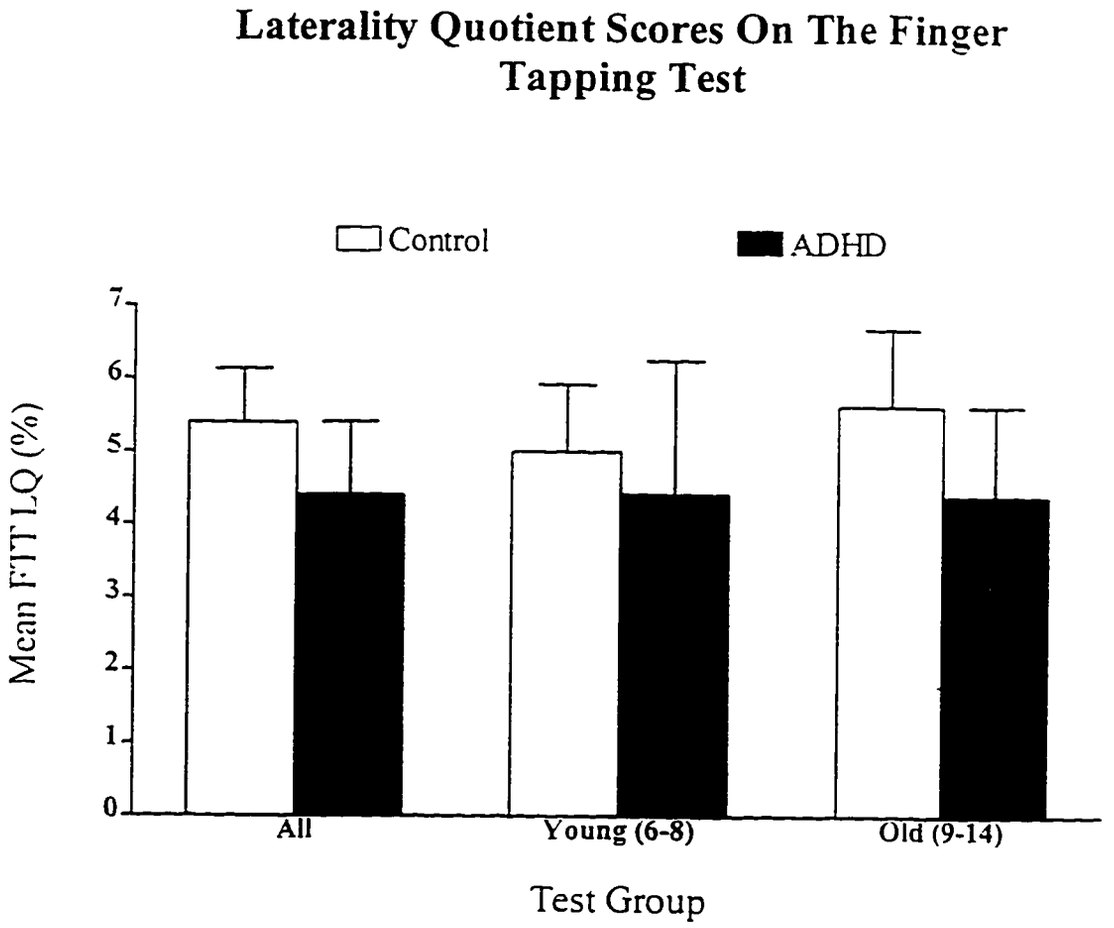


Figure 20: Bar chart comparing ADHD and control subjects on the Laterality Quotient measures of performance asymmetry ([{Pr-NP}/{Pr+NP}] X 100) on the FTT. Scores are presented for individual age subgroups and for total ADHD and control groups. Abbreviations are as follows: ADHD: attention deficit hyperactivity disorder, Pr: preferred hand, NP: non-preferred hand. FTT: finger tapping test, LQ: laterality quotient.

NP/Pr Intermanual Ratio Scores On The Finger Tapping Test

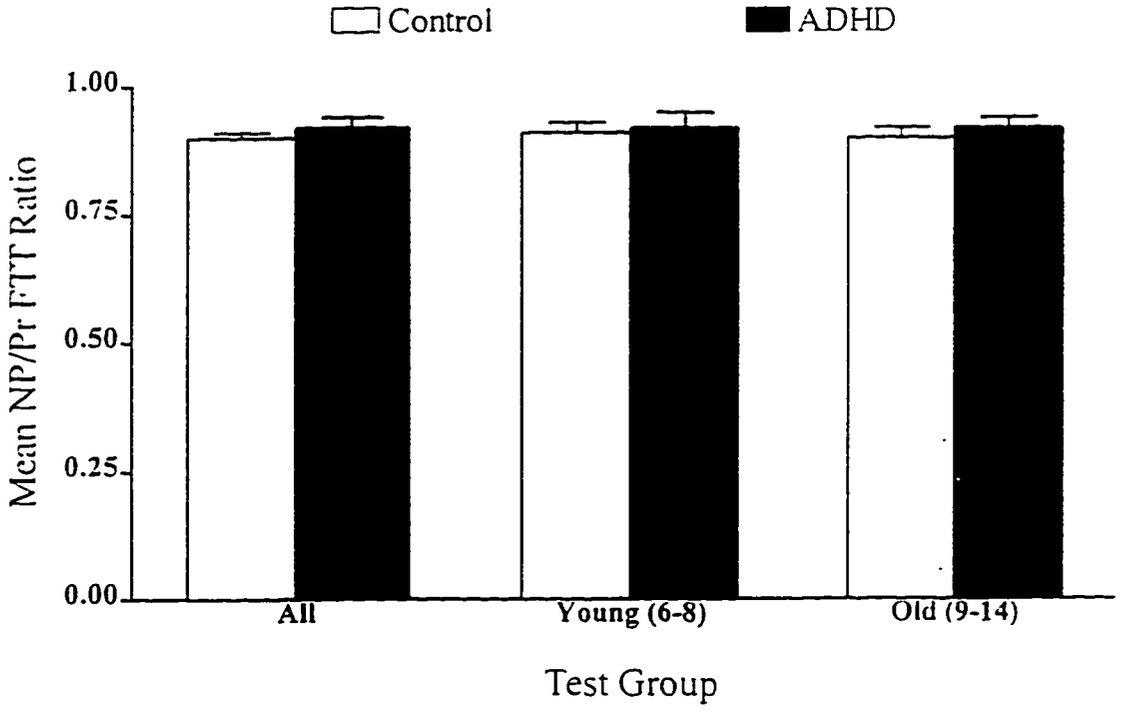


Figure 21: Bar chart comparing ADHD and control subjects on the NP/Pr measures of performance asymmetry on the FTT. Scores are presented for individual age subgroups and for total ADHD and control groups. Abbreviations are as follows: ADHD: attention deficit hyperactivity disorder, Pr: preferred hand, NP: non-preferred hand. FTT: finger tapping test.

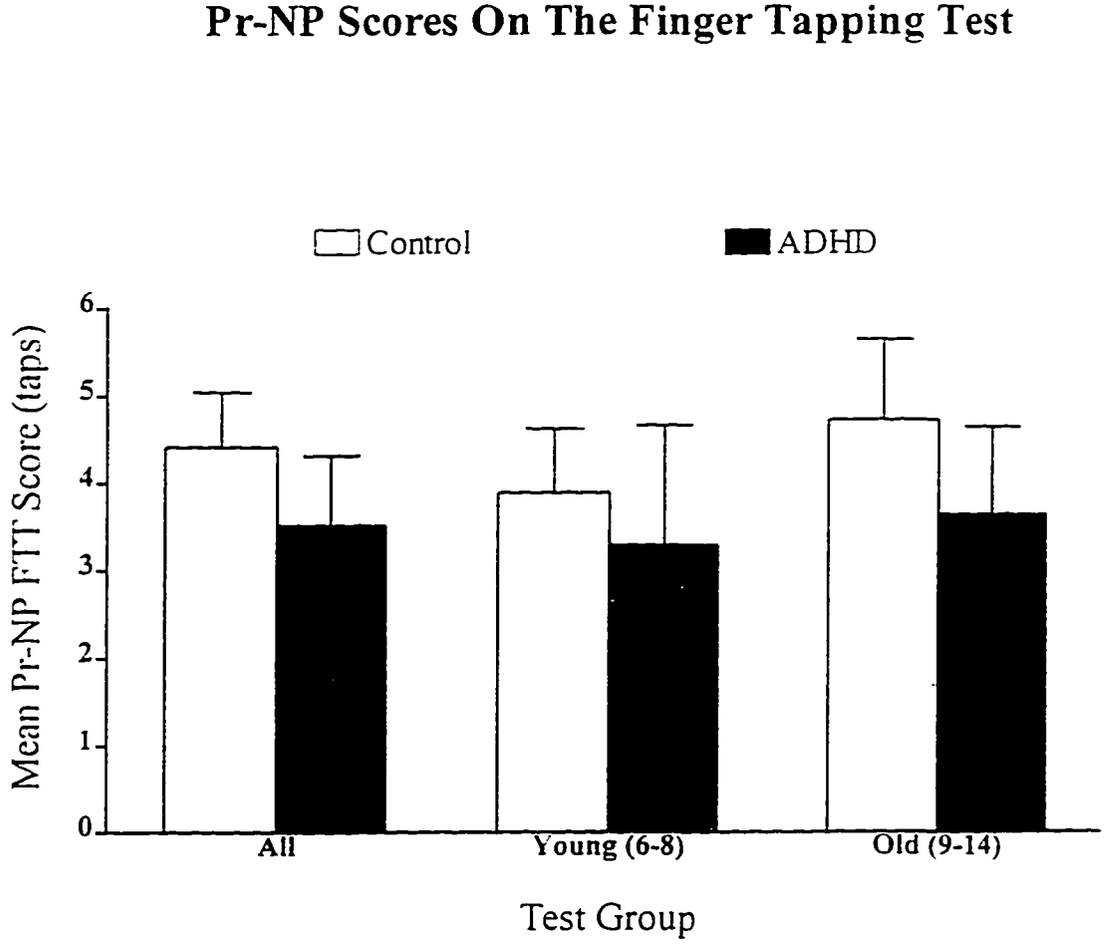


Figure 22: Bar chart comparing ADHD and control subjects on the Pr-NP measure of performance asymmetry on the FTT. Scores are presented for individual age subgroups and for total ADHD and control groups. Abbreviations are as follows: ADHD: attention deficit hyperactivity disorder, Pr: preferred hand, NP: non-preferred hand, FTT: finger tapping test.

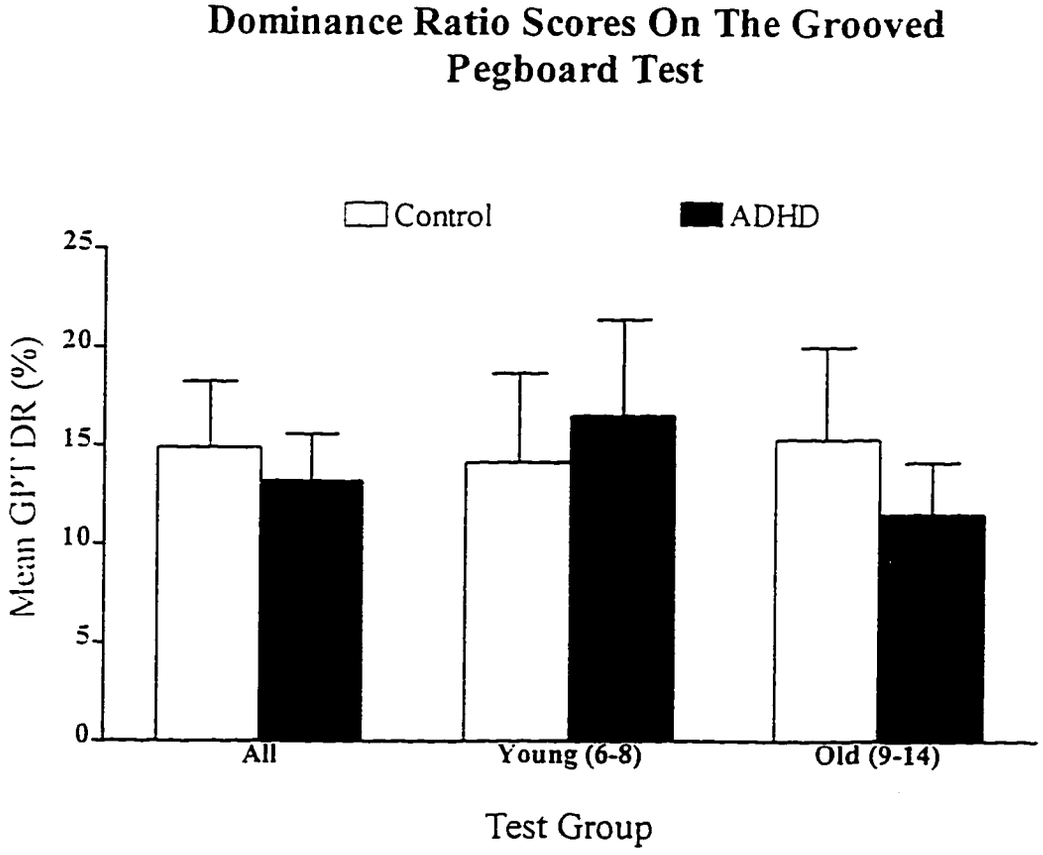


Figure 23: Bar chart comparing ADHD and control subjects on the Dominance Ratio measure of performance asymmetry on the GPT. Note that for calculation of performance asymmetry on the GPT, PR and NP scores need to be interchanged as higher scores indicate poorer performance on the GPT (Bornstein, 1986a): ((NP-Pr)/NP) X 100. Scores are presented for individual age subgroups and for total ADHD and control groups. Abbreviations are as follows: ADHD: attention deficit hyperactivity disorder, Pr: preferred hand, NP: non-preferred hand, GPT: grooved pegboard test, DR: dominance ratio.

Laterality Quotient Scores On The Grooved Pegboard Test

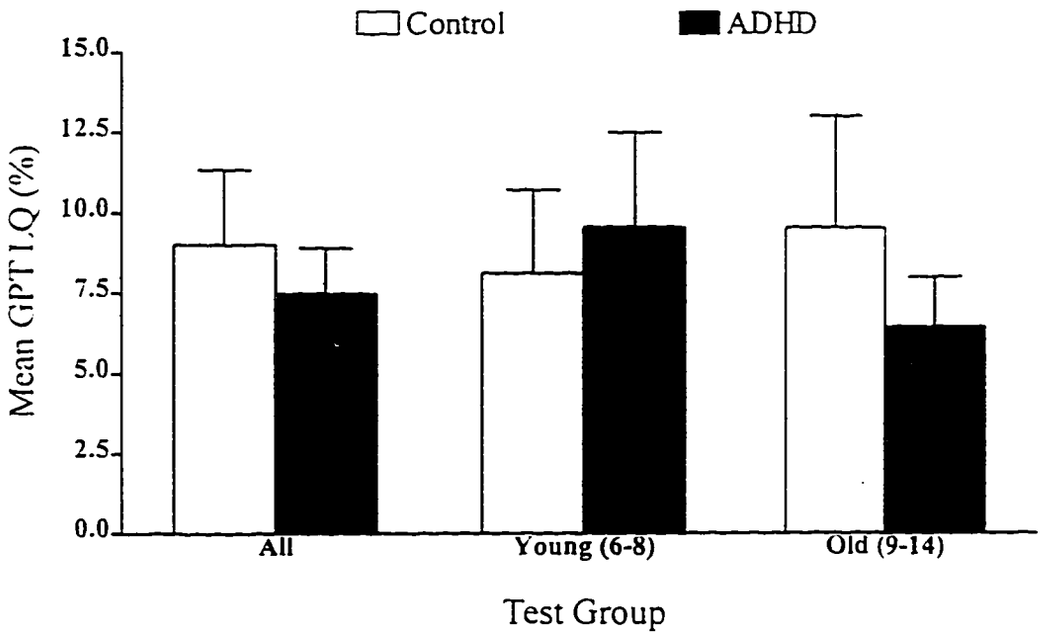


Figure 24: Bar chart comparing ADHD and control subjects on the Laterality Quotient measure of performance asymmetry on the GPT. Note that for calculation of performance asymmetry on the GPT, PR and NP scores need to be interchanged as higher scores indicate poorer performance on the GPT (Bornstein, 1986a): ((NP-Pr)/(NP+Pr)) X 100. Scores are presented for individual age subgroups and for total ADHD and control groups. Abbreviations are as follows: ADHD: attention deficit hyperactivity disorder, Pr: preferred hand, NP: non-preferred hand, GPT: grooved pegboard test, LQ: laterality quotient.

NP/Pr Intermanual Ratio Scores On The Grooved Pegboard Test

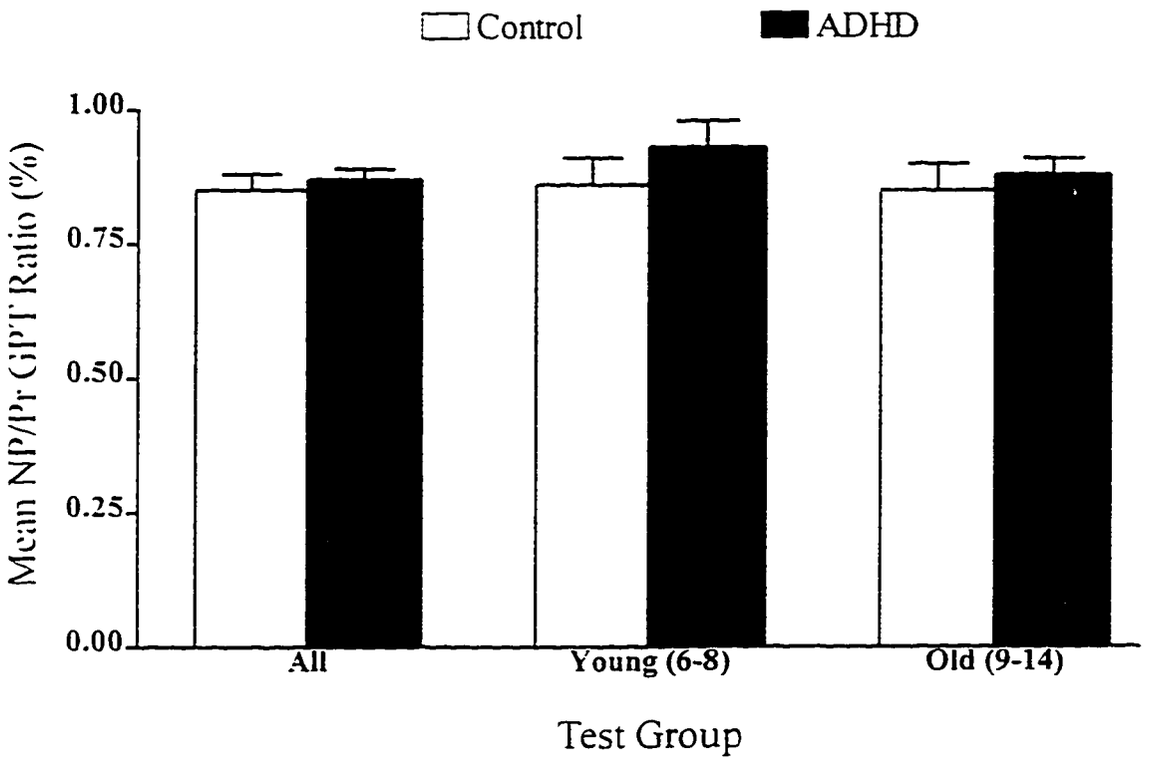


Figure 25: Bar chart comparing ADHD and control subjects on the Pr/NP measure of performance asymmetry on the GPT. Note that for calculation of performance asymmetry on the GPT, PR and NP scores need to be interchanged as higher scores indicate poorer performance on the GPT (Bornstein, 1986a): Pr/NP. Scores are presented for individual age subgroups and for total ADHD and control groups. Abbreviations are as follows: ADHD: attention deficit hyperactivity disorder, Pr: preferred hand. NP: non-preferred hand, GPT: grooved pegboard test.

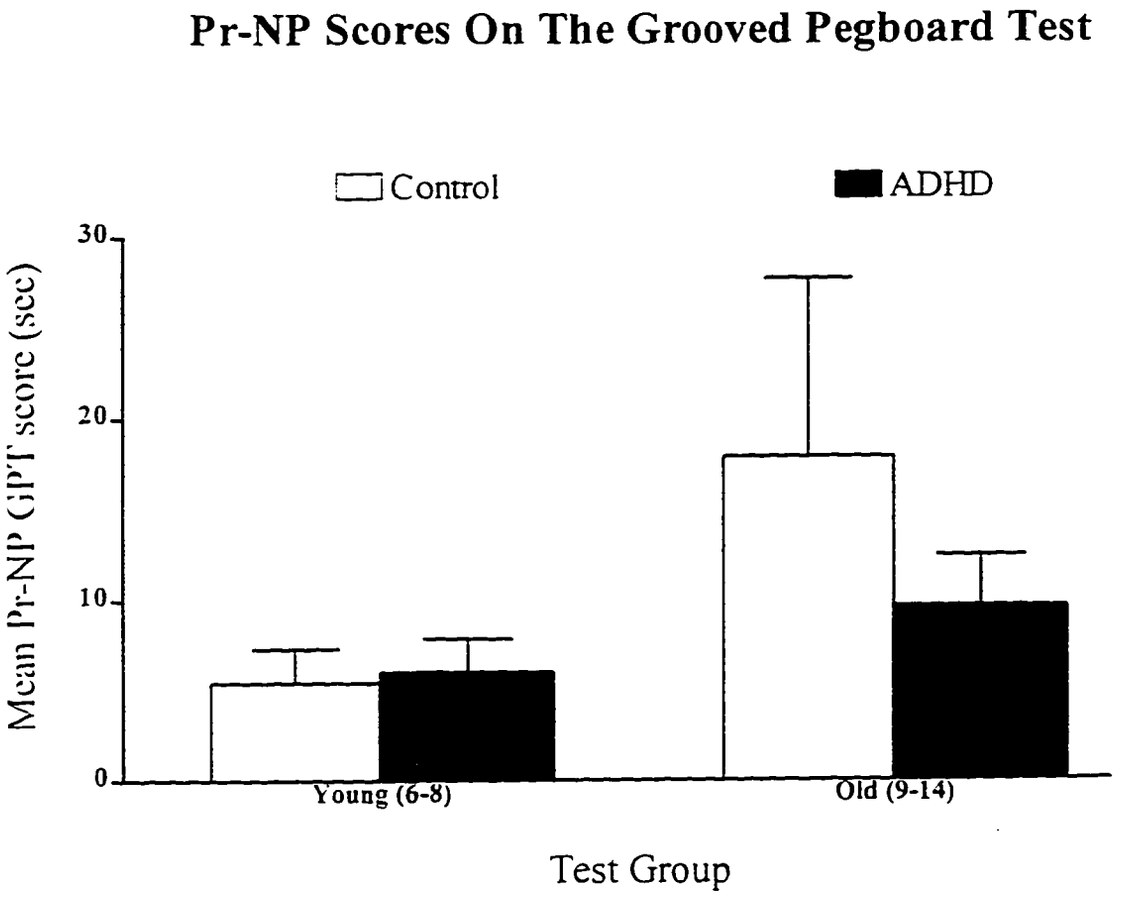


Figure 26: Bar chart comparing ADHD and control subjects on the NP-Pr measure of performance asymmetry on the GPT. Note that for calculation of performance asymmetry on the GPT, PR and NP scores need to be interchanged as higher scores indicate poorer performance on the GPT (Bornstein, 1986a): NP-Pr. Scores are presented for individual age subgroups and for total ADHD and control groups. Also notethet a mean 'All' group score could not be calculated due to different test administration procedures for different subgroups (see test administration procedures in text). Abbreviations are as follows: ADHD: attention deficit hyperactivity disorder, Pr: preferred hand, NP: non-preferred hand, GPT: grooved pegboard test, DR: dominance ratio, LQ: laterality quotient.

Dominance Ratio Scores On All Five Rows Of The Grooved Pegboard Test

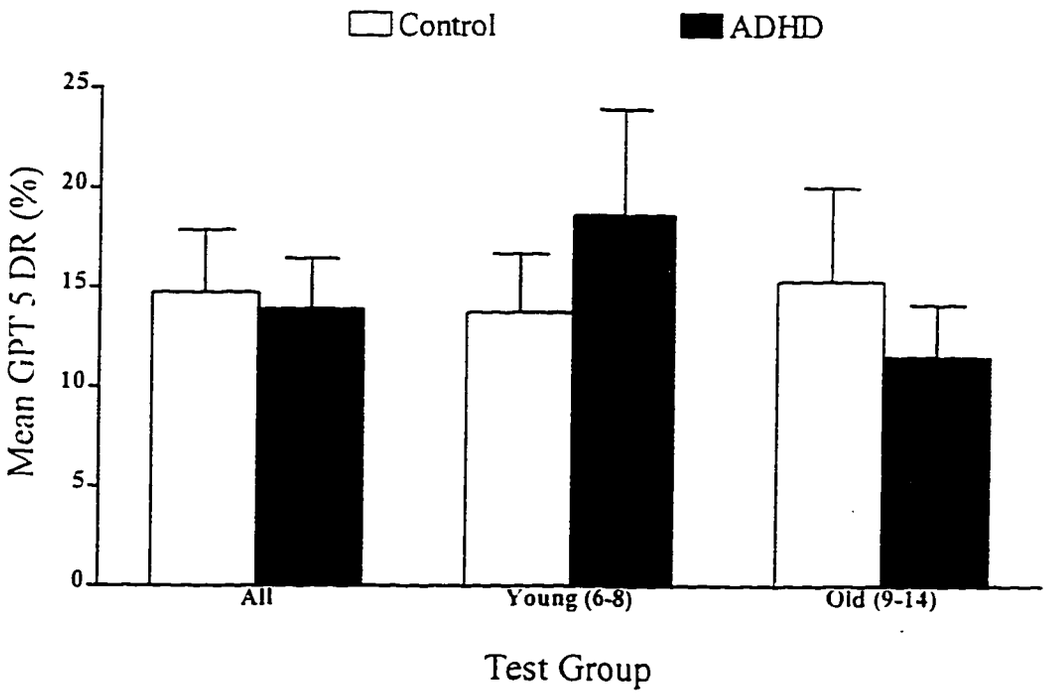


Figure 27: Bar chart comparing ADHD and control subjects on the Dominance Ratio measure of performance asymmetry on the GPT (all five rows). Note that for calculation of performance asymmetry on the GPT, PR and NP scores need to be interchanged as higher scores indicate poorer performance on the GPT (Bornstein, 1986a): ((NP-Pr)/NP) X 100. Scores are presented for individual age subgroups and for total ADHD and control groups. Abbreviations are as follows. ADHD: attention deficit hyperactivity disorder, Pr: preferred hand, NP: non-preferred hand, GPT 5: grooved pegboard test (all five rows), DR: dominance ratio.

Laterality Quotient Scores On All Five Rows Of The Grooved Pegboard Test

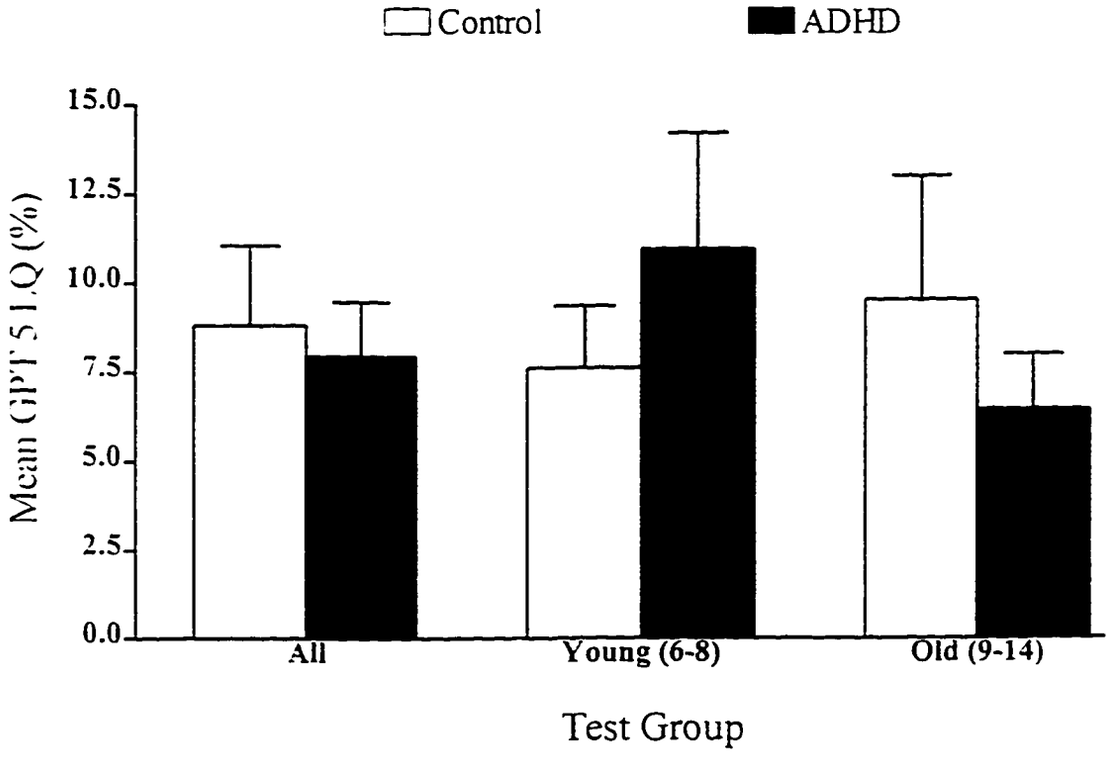


Figure 28: Bar chart comparing ADHD and control subjects on the Laterality Quotient measure of performance asymmetry on the GPT (all five rows). Note that for calculation of performance asymmetry on the GPT, PR and NP scores need to be interchanged as higher scores indicate poorer performance on the GPT (Bornstein, 1986a): ((NP-Pr)/(NP+Pr)) X 100. Scores are presented for individual age subgroups and for total ADHD and control groups. Abbreviations are as follows: ADHD: attention deficit hyperactivity disorder, Pr: preferred hand, NP: non-preferred hand, GPT 5: grooved pegboard test (all five rows), LQ: laterality quotient.

NP/Pr Intermanual Ratio Scores On All Five Rows Of The Grooved Pegboard Test

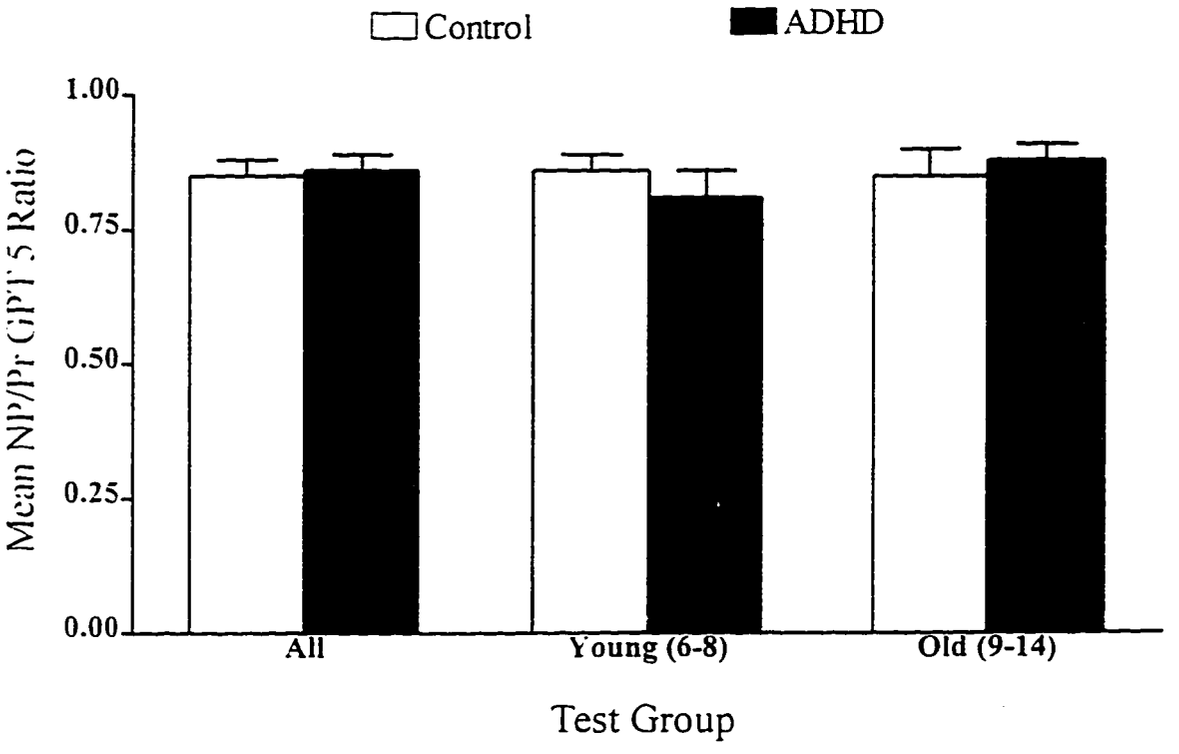


Figure 29: Bar chart comparing ADHD and control subjects on the Pr/NP measure of performance asymmetry on the GPT (all five rows). Note that for calculation of performance asymmetry on the GPT, PR and NP scores need to be interchanged as higher scores indicate poorer performance on the GPT (Bornstein, 1986a): Pr/NP. Scores are presented for individual age subgroups and for total ADHD and control groups. Abbreviations are as follows: ADHD: attention deficit hyperactivity disorder, Pr: preferred hand, NP: non-preferred hand, GPT 5: grooved pegboard test (all five rows).

Pr-NP Scores On All Five Rows Of The Grooved Pegboard Test

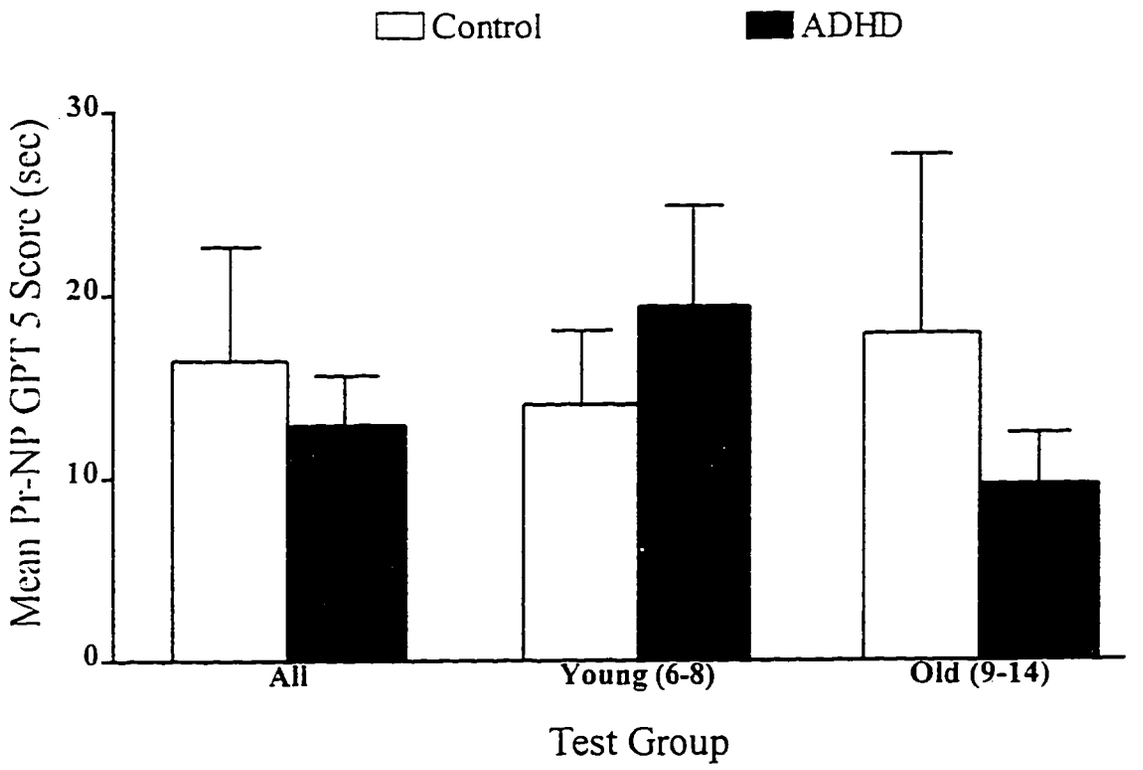


Figure 30: Bar chart comparing ADHD and control subjects on the NP-Pr measure of performance asymmetry on the GPT (all five rows). Note that for calculation of performance asymmetry on the GPT, PR and NP scores need to be interchanged as higher scores indicate poorer performance on the GPT (Bornstein, 1986a): NP-Pr. Scores are presented for individual age subgroups and for total ADHD and control groups. Abbreviations are as follows: ADHD: attention deficit hyperactivity disorder, Pr: preferred hand, NP: non-preferred hand, GPT 5: grooved pegboard test (all five rows).

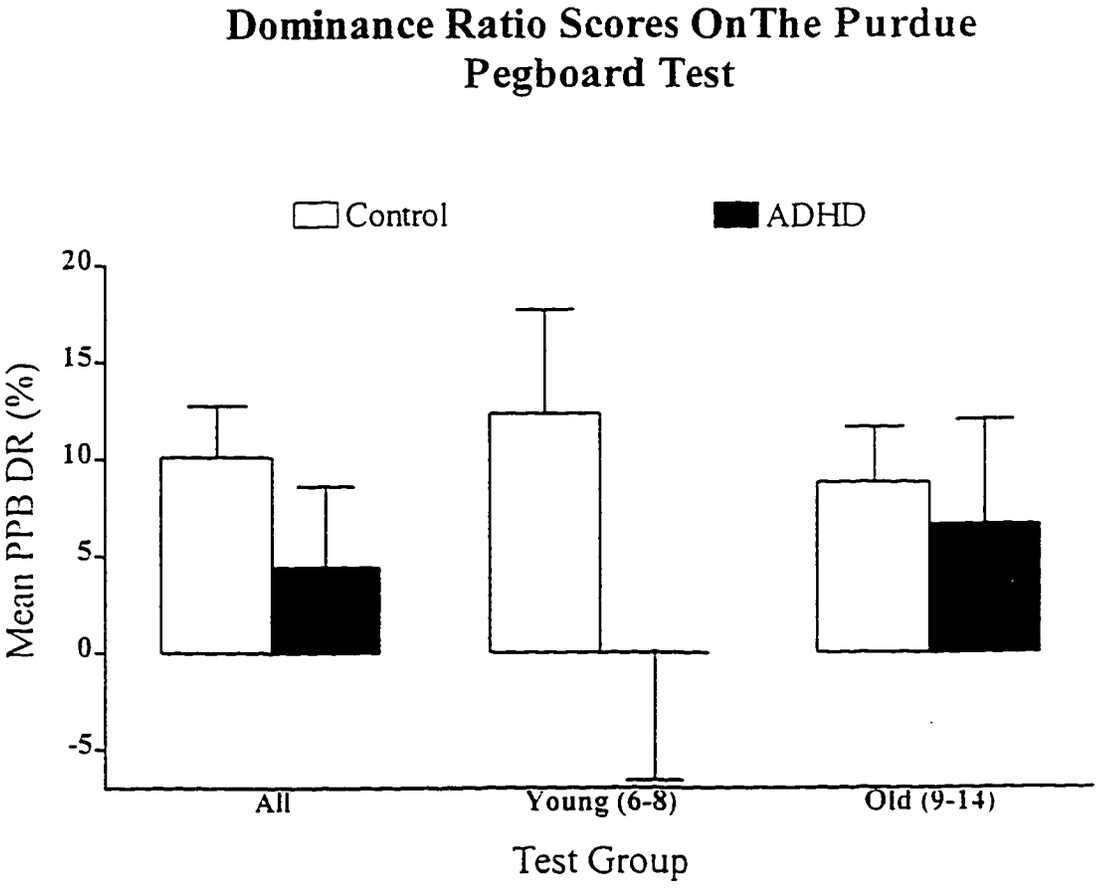


Figure 31: Bar chart comparing ADHD and control subjects on the Dominance Ratio measures of performance asymmetry ([{Pr-NP}/Pr] X 100) on the PPB. Scores are presented for individual age subgroups and for total ADHD and control groups. Abbreviations are as follows: ADHD: attention deficit hyperactivity disorder, Pr: preferred hand, NP: non-preferred hand. PPB: Purdue Pegboard, DR: dominance ratio.

Laterality Quotient Scores OnThe Purdue Pegboard Test

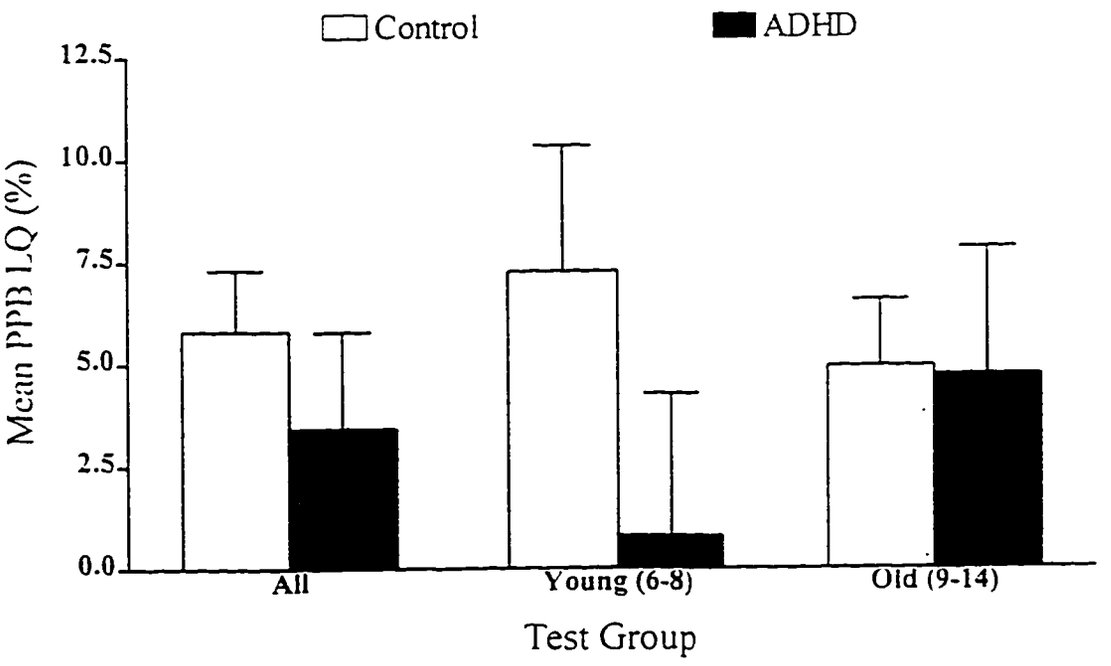


Figure 32: Bar chart comparing ADHD and control subjects on the Laterality Quotient measure of performance asymmetry ([{Pr-NP}/{Pr+NP}] X 100) on the PPB. Scores are presented for individual age subgroups and for total ADHD and control groups. Abbreviations are as follows: ADHD: attention deficit hyperactivity disorder. Pr: preferred hand. NP: non-preferred hand. PPB: Purdue Pegboard. LQ: laterality quotient.

NP/Pr Intermanual Ratio Scores On The Purdue Pegboard Test

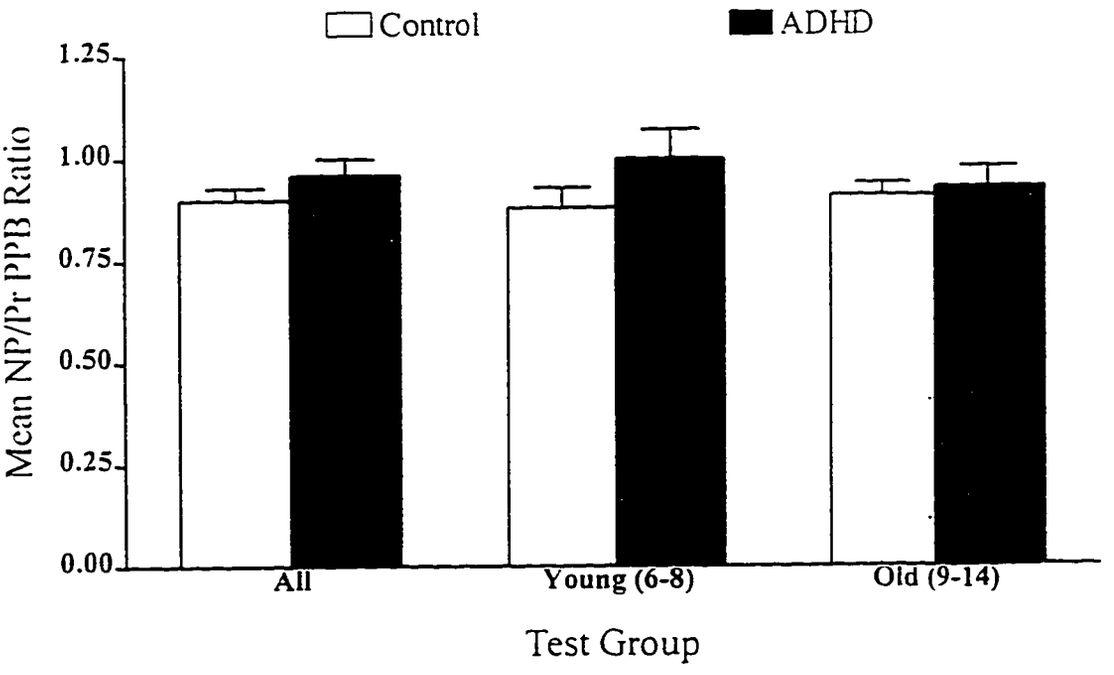


Figure 33: Bar chart comparing ADHD and control subjects on the NP/Pr measure of performance asymmetry on the PPB. Scores are presented for individual age subgroups and for total ADHD and control groups. Abbreviations are as follows: ADHD: attention deficit hyperactivity disorder, Pr: preferred hand, NP: non-preferred hand. PPB: Purdue Pegboard.

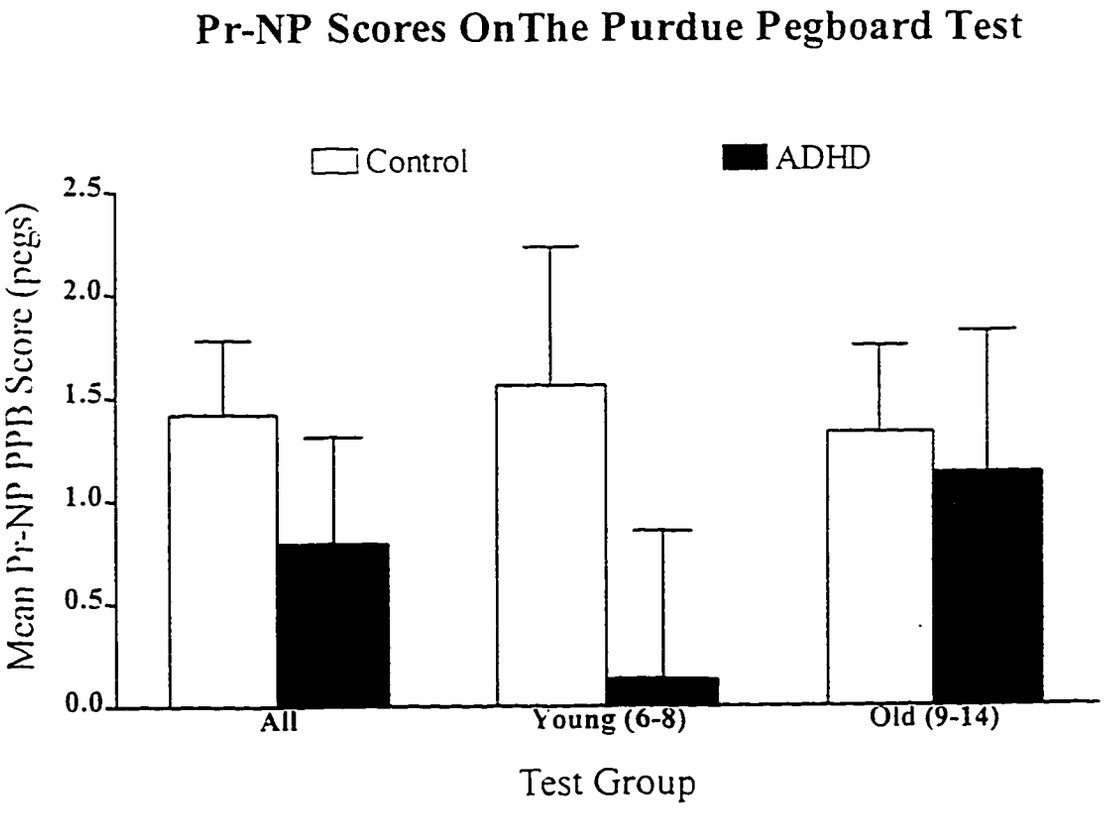


Figure 34: Bar chart comparing ADHD and control subjects on the Pr-NP measure of performance asymmetry on the PPB. Scores are presented for individual age subgroups and for total ADHD and control groups. Abbreviations are as follows: ADHD: attention deficit hyperactivity disorder, Pr: preferred hand, NP: non-preferred hand. PPB: Purdue Pegboard.

with χ^2 analysis or the Fisher Exact P statistic when all assumptions of χ^2 analysis could not be met (Siegel, 1956). The α level for these significance tests was lowered to $\alpha^* = .01$ to reduce the chance of obtaining type I errors (Krauth, 1988).

Table 6 and Figure 35 show the results comparing groups on the prevalence of asymmetry on the four motor tests used in this study. Significantly *fewer* ADHD subjects showed asymmetrical motor performance than controls on the GPT (χ^2 (1)= 8.40, $p < .01$). No significant differences between groups were found on any of the remaining motor tests.

The consistency of asymmetrical motor performance across all four tests was also calculated. This total asymmetry measure was compared between ADHD and control groups with the Mann-Whitney U test of significance. The adjusted the α level used for these significance tests was: $\alpha^* = .01$.

Table 7 and Figure 36 show that there was no significant difference between ADHD and control groups in consistency of asymmetrical motor performance.

Table 6: Percent of subjects in each group that show asymmetrical motor performance on the hand dynamometer (DYN), finger tapping test (FTT), grooved pegboard test (GPT), and Purdue pegboard (PPB).

Test	*CONTROL*	*ADHD*
DYN	45.8	66.7
FTT	12.5	33.3
GPT	58.3	29.2*
PPB	62.5	62.5

* indicates significantly different ($p<.01$) from control group

Table 7: Percent of subjects showing an asymmetrical motor performance all four motor tests in the present experiment.

Number of tests showing ASYM	*CONTROL*	*ADHD*
None (0)	0.0	8.3
One	25.0	25.0
Two	33.3	25.0
Three	37.5	33.3
Four (all)	4.2	8.3

ASYM- asymmetrical motor performance

Prevalence of Asymmetrical Motor Performance On Different Motor Tests

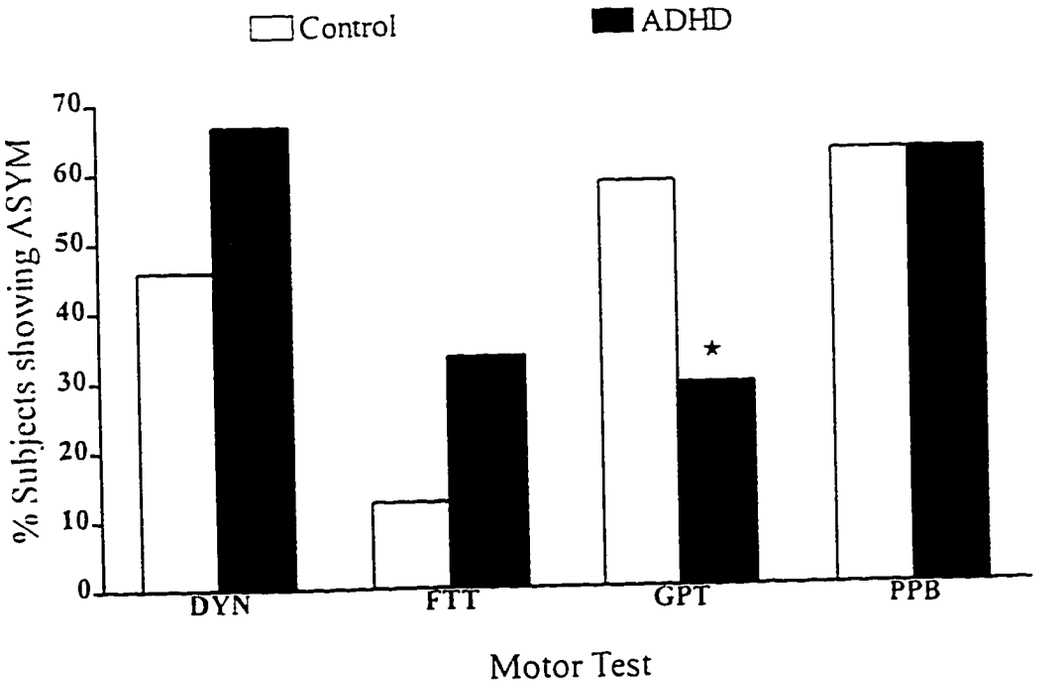


Figure 35: Bar chart comparing the percent of subjects demonstrating asymmetrical motor performance (score outside the 0-20% range on the dominance ratio score) on the four motor tests. ★ Indicates significantly different from controls ($p<.01$). Abbreviations are as follows: ADHD: attention-deficit hyperactivity disorder. ASYM: asymmetrical motor performance, DYN: hand dynamometer. FTT: finger tapping test. GPT: grooved pegboard. PPB: Purdue Pegboard.

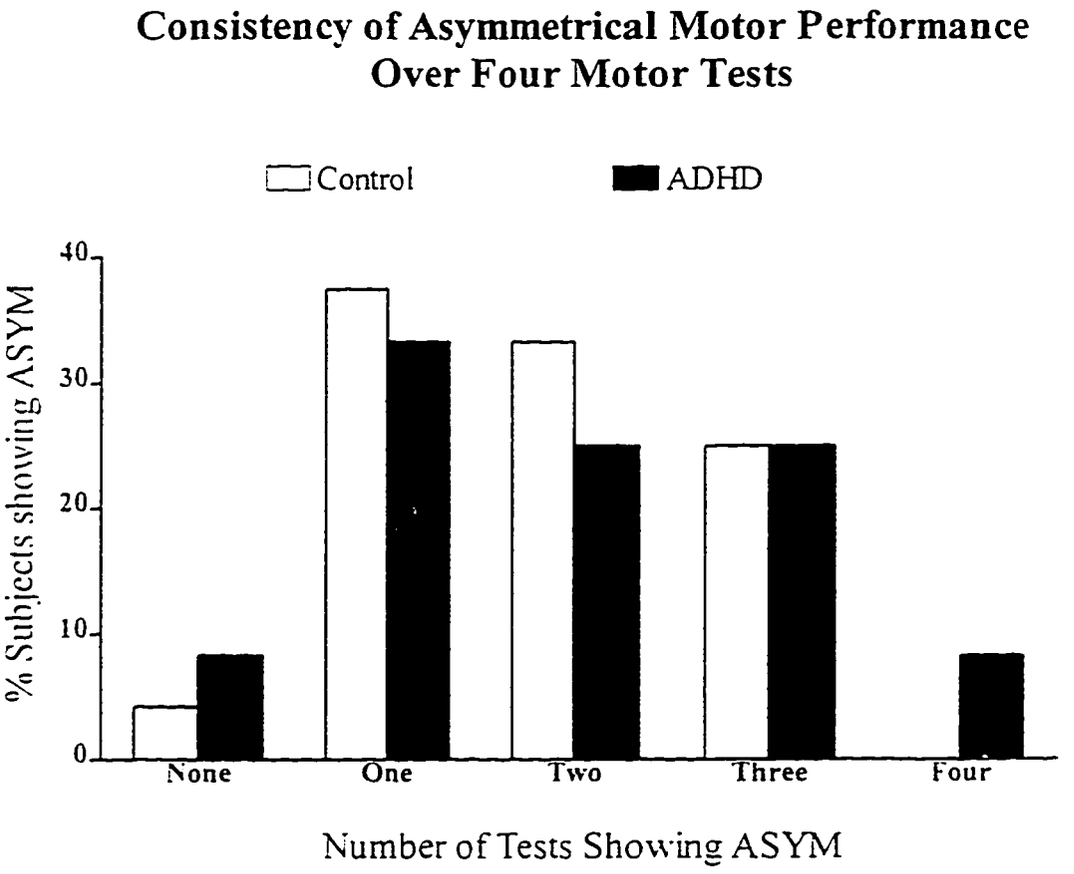


Figure 36: Bar chart comparing ADHD and control groups on consistency of asymmetrical motor performance (score outside the 0-20% range on the dominance ratio score) over all motor tests in the main study. Percent of subjects demonstrating ASYM is presented for both test groups. Abbreviations are as follows: ADHD: attention-deficit hyperactivity disorder, ASYM: asymmetrical motor performance.

D Discussion

In the present study, motor patterns of ADHD children were examined with four neuropsychological tests and compared to motor patterns of non-ADHD children. Grip strength was tested with the DYN, motor speed with the FTT, and fine motor dexterity was tested with the GPT and PPB. Not only performance, but *asymmetry* of performance was compared between subjects on these tests. With asymmetry measures, prevalence of asymmetrical motor performance for individual motor tests and consistency of asymmetrical motor performance over all motor tests was determined. The children with ADHD demonstrated significantly poorer performance of the PPB as compared to normal controls. Also, significantly fewer ADHD subjects showed asymmetrical motor performance on the GPT. These findings support the hypothesis that motor patterns of ADHD children would be significantly different from normal control children.

D.1 Purdue Pegboard

This study was the first to examine the performance of ADHD subjects on the PPB. Scores for the preferred hand on the PPB were significantly lower for ADHD subjects. On average, ADHD subjects' scores were 8.2% lower than normal controls' scores. The young subgroup of subjects demonstrated even a larger difference of 16.4%,

while the older subgroup did not differ significantly from controls. No differences were found between groups in asymmetry or prevalence of asymmetry on the PPB. Other researchers have found significant differences on the PPB in different patient populations. In a study on Down syndrome, Aylward et al. (1997) found that total brain volume is significantly correlated with performance on the PPB. Using CT, Nasrallah et al. (1986) found that 58% of young adult subjects with hyperkinesis and minimal brain dysfunction (an early diagnosis of ADHD) demonstrated mild to moderate cortical atrophy as evidenced by sulcal widening. Using the better resolution of MRI, Castellanos et al. (1994, 1996) have quantified ADHD brain atrophy by finding five percent less total brain volume as compared to normal controls. A report by Sauerwein and Lassonde (1994) demonstrated that subjects with callosal agenesis (congenitally without a corpus callosum) have scores on average 74.6% lower than normal controls on the PPB. Studies using MRI to study the morphology of the corpus callosum have found structural abnormalities in ADHD subjects (Hynd et al., 1991; Semrud-Clikeman et al., 1994; Geidd et al., 1994; Baumgartner et al., 1996; Lyoo et al., 1996). Many studies have found ADHD subjects have a 10-13% smaller splenium as compared to normal subjects (Hynd et al., 1991; Semrud-Clikeman et al., 1994; Lyoo et al., 1996). Some of these studies have also found 20% smaller area of the

posterior midbody/isthmus region (Hynd et al., 1991) and 17% smaller area of the isthmus (Lyoo et al., 1996). The posterior regions of the corpus callosum (posterior midbody, isthmus, and splenium) interconnect the somatosensory, superior temporal, posterior parietal and inferior temporal parts of the cerebral cortex (Geidd et al., 1994). The primary function of the posterior corpus callosum in motor function is allowing the transfer of sensory feedback between the hemispheres (Geffen et al., 1994).

Differences between ADHD and non-ADHD subjects have also been found in the anterior region of the corpus callosum. Subjects with ADHD have been found to have a 13-15% smaller rostral body as compared to non-ADHD subjects (Baumgartner et al., 1996; Geidd et al., 1994). The rostral body interconnects the supplementary motor area, and premotor, prefrontal, and anterior cingulate cortices (Geidd et al., 1994; Steere and Arnsten, 1995). The genu (16%; Hynd et al., 1991) and rostrum (27%; Geidd et al., 1994) are other anterior regions of the corpus callosum that are smaller in ADHD subjects. The rostrum interconnects the caudal/orbital prefrontal and inferior premotor cortices while the genu interconnects prefrontal cortices (Geidd et al., 1994). Now, while the corpus callosum is not entirely absent in ADHD subjects (as in subjects with callosal agenesis), a

malformed callosum should lead to a less dramatic, yet, measurable deficit in motor control. The present study supports this view as ADHD subjects' performance on the PPB (by 8.2%) is not as severe as the deficit shown in subjects without a corpus callosum (74.6%; Sauerwein and Lassonde, 1994).

Areas of the anterior and posterior corpus callosum appear to be abnormal in ADHD subjects (Baumgartner et al., 1996; Geidd et al., 1994; Lyoo et al., 1996; Semrud-Clikeman et al., 1994; Hynd et al., 1991). The area that is most pertinent to PPB performance can be determined by examining other studies that have correlated neuropsychological performance with callosal section or malformation (Pelletier et al., 1993). A study on multiple sclerosis patients determined that the area (size) of the anterior corpus callosum is associated with performance of a finger tapping task (Pelletier et al., 1993). In the present study, ADHD and normal controls did not significantly differ on any measure of the FTT. Generalizing from the results of Pelletier et al.'s study, since no deficit was found on the FTT, a test that requires an intact anterior corpus callosum to be performed accurately, it can be assumed that this callosal region was not significantly abnormal in the ADHD group in the present study. However, abnormalities of the corpus callosum *do* influence PPB

performance (Sauerwein and Lassonde, 1994). Since PPB performance is affected in ADHD subjects, it can be postulated that an intact *posterior* region of the corpus callosum is required for accurate performance of the PPB. From this, as the posterior region is responsible for the transfer of sensory feedback information (Geffen et al., 1994), sensory input is necessary for accurate performance of the PPB. Since ADHD subjects performed poorly on the PPB, it can be postulated that there is a deficit in sensory processing in ADHD subjects that may be linked to the inattentive and/or impulsive-hyperactive aspects of the disorder. Further research correlating callosal measures to neuropsychological performance in ADHD subjects will be necessary to verify this hypothesis.

D.2 Grooved Pegboard Test

This study was the first to compare prevalence of asymmetry between ADHD and normal control children. Results of prevalence of asymmetry measures found significantly fewer ADHD subjects demonstrating dominance ratio scores outside the 0-20% range on the GPT. Whereas 58.3% of normal subjects demonstrated dominance ratios outside of this range, only 29.2% of ADHD subjects fell outside this range. No differences were found between ADHD and control groups in GPT performance or performance asymmetry. This is in

agreement with most other studies that have tested the performance of ADHD subjects on the GPT (Barkley et al., 1992; Yeates and Bornstien, 1994). However, in a pilot study, Panich et al. (1994) found a significant difference in GPT performance asymmetry between ADHD and normal children. This finding was not replicated in the present study for any measure of performance asymmetry. Neither this nor the pilot study (Panich et al., 1994) controlled for presence of learning disorders or family history of ADHD, both of which influence motor performance in ADHD (Seidman et al., 1995). This may have been a contributing factor to the discrepancy between the present and pilot (Panich et al., 1994) studies.

Studies on patients infected with the human immunodeficiency virus have found a correlation between caudate nuclei volume and area and scores on the GPT (Keiburtz et al., 1996; Hestad et al., 1993). These studies have significantly correlated GPT scores with caudate area and volume (Keiburtz et al., 1996; Hestad et al., 1993). MRI studies on ADHD subjects have found between 2.4-19% smaller caudate nucleus area and volume (Hynd et al., 1993; Castellanos et al., 1994, 1996). Furthermore, the paired caudate nuclei demonstrate less structural asymmetry in ADHD subjects than in normal controls (Castellanos et al., 1994, 1996). Studies have found the asymmetry of motor

structures in the human brain is related to outward motor patterns (Foundas et al., 1995b, 1996; White et al., 1994; Kooistra and Heilmann, 1988). White et al. (1994) examined the dorsolateral surface of the central sulcus (the border between the primary sensory and motor areas of the brain) adult brains post-mortem. This study found the left side to be on average 7.2% larger than the right and the difference was more pronounced in the region representing the upper extremities (hand). Later research by Foundas et al. (1995b, 1996) advanced this finding by relating a leftward asymmetry of the motor bank of the central sulcus to right-handedness. Kooistra and Heilman (1988) found a left > right asymmetry of the globus pallidus in 18 normal post-mortem brains. The researchers suggested that the leftward asymmetry of the globus pallidus may relate to limb motor dominance. Caudate area and volume have been related to performance on the GPT and the caudate nuclei show reduced asymmetry in ADHD subjects. Therefore, as asymmetry of motor structures is related to outward motor patterns it can be postulated that reduced caudate asymmetry might be responsible for the reduced prevalence of GPT asymmetry in ADHD subjects.

Numerous researchers have focused on the role of frontostriatal circuitry in ADHD (Casey et al., 1997; Heilman et al., 1991; Voeller,

1991). Through lesion studies in humans and laboratory animals, researchers have proposed that this circuitry is responsible for response inhibition, sustained attention, verbal learning and memory, and executive function (organization and complex problem solving) (Heilman et al., 1991, Voeller, 1991, Casey et al., 1997). Barkley (1997) has proposed the core deficit in ADHD to be that of behavioral inhibition and from this deficit all other problems in executive function arise. The link between the caudate nucleus and performance on the GPT may be a result of the deficit in behavioral inhibition as proposed by Barkley (1997).

Both the GPT and PPB are pegboard tests that measure fine visually guided motor skills (Trites, 1977; Aylward et al., 1997; Barkley et al., 1992). However, in the present study, both tests did not reveal similar results from the same subject group. As this may be the first study to use both the GPT and PPB to test the same group of subjects, this finding may be of some importance. Since the results of both tests were not similar, it can be postulated that each test measures a different aspect of fine visually guided movements. Further research on these tests should focus which precise areas of motor control are being tested with each test.

D.3 Finger Tapping Test

The present study found no significant findings on any measure of the FTT. This lack of significant findings on the FTT supports the findings of other researchers that tested finger tapping in ADHD subjects (Seidman et al., 1995, 1997a; Yeats and Bornstein, 1994; Panich et al., 1994; Arcia and Gualtieri, 1994). Seidman et al.'s 1995 study *did* find FTT performance significantly different between a subgroup of ADHD subjects with learning disorders and normal controls. However, the present study did not clinically determine the presence of learning disorders in the subject population thus making direct comparison to Seidman et al.'s (1995) study impossible.

There have been many studies relating brain structure and function to performance of finger tapping (Pelletier et al., 1994; Mercuri et al., 1996; Kieburtz et al., 1996; Saurewein and Lassonde, 1994; Lauritzen et al., 1981; Hokama et al., 1995; Paradiso et al., 1997). Studies on patients with multiple sclerosis (Pelletier et al., 1994) and 'clumsy' children born prematurely (Mercuri et al., 1996) have found positive correlations between area (size) of the corpus callosum and finger tapping performance. Furthermore, a study on subjects with callosal agenesis found on average 32.3% lower scores on the FTT (Saurewein and Lassonde, 1994). Studies have shown abnormal corpus callosum

structure in ADHD subjects (Hynd et al., 1991; Baumgartner et al., 1996; Geidd et al., 1994; Lyoo et al., 1996; Semrud-Celikeman et al., 1994). As discussed earlier, the anterior corpus callosum is the area most likely to be responsible for FTT performance (Pelletier et al., 1994). Since FTT performance was not significantly different from normal controls it may be that this area is not significantly abnormal in the ADHD group in the present study.

A study measuring CBF in normal subjects found activation of the contralateral primary motor cortex and supplementary motor area during finger tapping (Lauritzen et al., 1981). SPECT studies on ADHD children have shown 9.6% more perfusion of the left sensorimotor cortex than normal controls (Lou et al., 1989). However, the FTT scores of ADHD subjects in the present study were not significantly different from normal controls. From this, it may be that CBF in the primary motor cortex and supplementary motor area was not significantly different from normal controls in the present sample of ADHD subjects.

A MRI study measuring caudate, putamen, and globus pallidus volume in normal and schizophrenic patients found lower preferred hand performance on the FTT was associated with a larger right and

left caudate volume (Hokama et al., 1995). This same study found larger right globus pallidus volume to be associated with lower FTT scores on the non-preferred hand (Hokama et al., 1995). Another study on patients infected with the human immunodeficiency virus found *no correlation* between caudate volume and FTT performance (Kieburtz et al., 1996). MRI studies of basal ganglia structure in ADHD subjects have found reduced volume of both the caudate and globus pallidus (Castellanos et al., 1994, 1996; Aylward et al., 1996; Hynd et al., 1993; Singer et al., 1993). Since caudate and pallidal volumes are smaller than normal in ADHD subjects, according to the Hokama et al. (1995) study, these subjects would not be expected to perform differently from normal controls as low caudate and/or globus pallidus volumes were not correlated with lower FTT scores. The results of the present study support this view as ADHD subjects' scores were not significantly different from normal controls. Therefore, the present sample of ADHD subjects may not have had significantly larger caudate or globus pallidus volumes as compared to normal controls.

A study correlating neuropsychological tests with cerebellar size found a significant positive correlation between FTT scores and cerebellar volume (Paradiso et al., 1997). In ADHD subjects cerebellar volume is

about 9.0% less than normal subjects (Castellanos et al., 1996). Yet, with this alteration, no significant differences were found between normal and ADHD subjects on the FTT in the present experiment.

It seems likely that all of the above listed abnormalities in neural structure found in ADHD subjects will result in a measurable influence on motor control. It is probable that the lack of significant findings on the FTT for ADHD subjects reflects a lack of sensitivity of the FTT to motor deficits that result from the structural and functional aberrations shown in ADHD subjects (also see: Keiburtz et al., 1996). Studies directly correlating neural structure in ADHD to performance on neuropsychological tests are needed to clarify the influence of abnormalities in regions responsible for motor control and neuropsychological test performance.

D.4 Hand Dynamometer

No difference between ADHD and normal control subjects was found on any measure of performance of the DYN in the present study. This is the first study to examine the performance of ADHD subjects on the DYN. Amount of force exerted in movement is encoded by the primary motor cortex (Ghez, 1991a) an area shown to be abnormal in some ADHD subjects (Lou et al., 1989; Hynd et al., 1990; Castellanos et al.,

1994, 1996). As the DYN is a motor test that measures grip strength (Spreen and Strauss, 1991), poor performance on this test should indicate dysfunction of this area of the brain. However, the performance of ADHD subjects on the DYN did not differ significantly from normal controls in the present study. The primary motor cortices are interconnected by the anterior portion of the corpus callosum (Geidd et al., 1994). A study on subjects with callosal agenesis found 44.8% lower scores on the DYN as compared to normal controls. A reduction in DYN scores would be expected from subjects having an abnormal corpus callosum. However, ADHD subjects did not differ from normal controls on the DYN. Earlier in this section, it was postulated that this area does not seem to be significantly altered in the present subject sample as determined by examining the results from the FTT and PPB. As a result, there is also no significant differences on the DYN either. It is not that the aberrant neural structure has no influence on motor patterns. As with the FTT, it is more likely that the DYN, too, is not sensitive to the deficits in motor control in ADHD.

D.5 Overview and Caveats

A major advantage of the present study is in the statistical control of type I error due to numerous statistical comparisons. This is not the

norm for studies on ADHD (Zametkin et al., 1990, 1993; Matochik et al., 1993, 1994; Ernst et al., 1994a, 1994b; Seidman et al., 1995, 1997a, 1997b; Yeates and Bornstein, 1994; Arcia and Gualtieri, 1994; Panich et al., 1994). Such statistical control in the present study further emphasizes the significance of the findings.

Some reasons behind the lack of significant findings on some measures could be related to subject classification. The present study did not assess presence of learning disorders or family history of ADHD both of which have been shown to influence performance on neuropsychological tests (Seidman et al., 1995). More precise classification of subjects in this manner may identify subgroups of ADHD subjects that may perform worse on neuropsychological motor measures than others. Such findings could assist clinicians classify ADHD subgroups that may respond better to certain types of medications or management strategies.

Replication of the results of this study may have a direct influence on the diagnosis and treatment of ADHD in clinical practice. If all ADHD subjects consistently demonstrate inferior preferred hand performance on the PPB, this score could be used as a standardized quantifiable neuropsychological test to define ADHD. If only a certain subset of

ADHD subjects show impaired performance on the PPB (i.e.: family history or comorbid conditions), then defining a subset of ADHD with the PPB could be used to guide treatment and management of ADHD symptoms. Finally, a better understanding of motor patterns in ADHD will give researchers a better understanding of the disorder and provide insight into better ways of treatment and management for patients with ADHD.

There have been no neuroimaging studies to date that examine the differences between ADHD subjects with and without learning disorders and/or family history of ADHD. As these factors can influence motor control (Seidman et al., 1995) there may be some specific neural abnormalities associated with a family history of ADHD or presence of a learning disorder. Studies directly correlating neuroanatomical and neurofunctional imaging with neuropsychological test performance results of sub-classified ADHD subjects would be extremely beneficial in understanding the contribution of neural aberrations to motor patterns in ADHD.

E SUMMARY

The present study was performed to analyze the motor patterns of ADHD children. Neuroimaging studies have found altered neural structure and function of brain areas responsible for motor control in studies of ADHD subjects. From this it was hypothesized that motor patterns in ADHD subjects would also be different from normal controls. Subjects performed four motor tests (FTT, DYN, PPB, and GPT) and were compared on measures of performance and asymmetry of performance. The present study is one of the first to analyze the asymmetry of performance on neuropsychological tests in ADHD subjects. This study also was the first to measure the prevalence and consistency of asymmetries in ADHD subjects on the four motor tests. The results of this study revealed that ADHD subjects perform significantly worse on the PPB as compared to normal controls. Examination of specific PPB variables demonstrated that performance with the preferred hand was significantly worse in ADHD subjects. When age subgroups were analyzed, the finding of lower PPB scores followed the young but not old subgroup. No differences in performance were found on any of the remaining motor tests. While no differences in performance asymmetry measures between ADHD and normal control subjects were found, significantly fewer ADHD subjects showed an asymmetrical motor pattern on the GPT. No

further differences were found between ADHD and normal control subjects in prevalence or consistency of asymmetry on the remaining motor tests. The results of this study offer partial confirmation of the hypothesis that motor patters would differ between ADHD and control subjects.

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Appendix A

Ethics Approval Forms obtained from the Research Ethics Board, Office of the Dean of the Faculty of Medicine and Oral and Health Sciences for 1994-1995, 1995-1996, and 1996-1997.

Office of the Dean
Faculty of Medicine

2J2.00 WC Mackenzie Health Sciences Centre
Telephone (403) 492-6621
FAX: (403) 492-7303

RESEARCH ETHICS BOARD

ETHICS APPROVAL FORM

Date: June 1994

Name(s) of Principal Investigator(s): Dr. Thomas Snyder

Department: Psychiatry

Title: Attention Deficit Hyperactive Disorder and Lateralized Motor Control.

The Research Ethics Board (REB) has reviewed the protocol involved in this project which has been found to be acceptable within the limitations of human experimentation. The REB has also reviewed and approved the patient information materials and consent form.

Specific Comments:

Signed - Chairman of Research Ethics Board

for the Faculty of Medicine
University of Alberta

This approval is valid for one year.

#Issue 1594

Office of the Dean
Faculty of Medicine

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RESEARCH ETHICS BOARD

ETHICS APPROVAL FORM

Date: June 1995

Name(s) of Principal Investigator(s): Dr. Thomas Snyder

Department: Psychiatry

Title:

Attention Deficit Hyperactive Disorder and Lateralized Motor Control.

The Research Ethics Board (REB) has reviewed the protocol involved in this project which has been found to be acceptable within the limitations of human experimentation. The REB has also reviewed and approved the patient information materials and consent form.

Specific Comments:

Signed - Chairman of Research Ethics Board

for the Faculty of Medicine
University of Alberta

This approval is valid for one year.

#Issue 1594

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RESEARCH ETHICS BOARD

ETHICS APPROVAL FORM

Date: June, 1996

Name(s) of Principal Investigator(s): Dr. Thomas Snyder

Department: Psychiatry

Title: Attention Deficit Hyperactive Disorder and Lateralized Motor Control.

The Research Ethics Board has reviewed the protocol involved in this project which has been found to be acceptable within the limitations of human experimentation. The REB has also reviewed and approved the patient information materials and consent form

Specific Comments:

Signed - Chairman of Research Ethics Board

for the Faculty of Medicine
University of Alberta

This approval is valid for one year.

Issue #1594

Appendix B

Information Sheet and Consent Form for the present study

Walter C. Mackenzie Health Sciences Centre

Aberhart Centre

University Hospitals Education and Development Centre

University Hospitals Outpatient Residence

[illegible] Patient Support Centre

8440 - 112 Street, Edmonton, Alberta, Canada, T6G 2B7 Tel: (403) 492-8822

INFORMATION SHEET

Attention Deficit Hyperactivity Disorder and Lateralized Motor Control

Principal Investigator: Dr. Thomas J. Snyder, Psychiatry

Co-Investigator(s): Dr. Sergio L. Schmidt, Psychology, U of A
Darrell J. Panich, Psychiatry, U of A

Purpose: You/your child are being invited to participate in a research study to determine the relationship between handedness and Attention Deficit Hyperactivity Disorder (ADHD).

This study is being done because a region of the brain involved in use of the hands is also believed to be involved in the hyperactive behaviours characteristic of ADHD. By coming to a better understanding of the relationship of handedness to hyperactivity, a more accurate diagnosis of children with and without hyperactivity may be possible. More specific drug treatment for children with and without hyperactivity may also be possible.

Procedure: You/your child will be briefly assessed by questionnaires for your hand preferences and the probability of ADHD and hyperactivity. Your child will then be asked to perform four tests of manual skill for a total time of approximately 25 minutes, two computer tasks of attention for another 25 minutes, and an auditory attention task for about 10 minutes.

Possible benefits: If information useful to your child's education or treatment is found, this information will be made available to you and appropriate professionals (family physician, educators, etc.) if you wish.

Possible risks: There are no risks associated with the procedures that are planned.

Confidentiality: Personal records relating to this study will be kept confidential. Any report published as a result of this study will not identify you/your child by name.

You/your child are free to withdraw from this research study at any time, and you/your child's continuing medical care will not be affected in any way. If the study is not undertaken or if it is discontinued at any time, the quality of you/ your child's medical care will not be affected. If any knowledge gained from this or any other study becomes available which could influence you/your child's decision to continue in the study you/your child will be promptly informed.

Please contact any of the individuals identified below if you have any questions or concerns:

Dr. Thomas J. Snyder, Assistant Clinical Professor of Psychiatry
492-8329

Darrell J. Panich, Department of Psychiatry, University of Alberta
(hm) 433-4496

Walter C. Mackenzie Health Sciences Centre

Aberhart Centre

University Hospitals Education and Development Centre

University Hospitals Outpatient Residence

[illegible] Parent Support Centre

8440 - 112 Street, Edmonton, Alberta, Canada, T6G 2B7 Tel: (403) 492-8822

CONSENT FORM

Title of Project:	Attention Deficit Hyperactivity Disorder and Lateralized Motor Control	
Principal Investigator:	Dr. Thomas J. Snyder - Psychiatry	492-8329
Co-Investigator(s):	Dr. Sergio L. Schmidt - Psychology	492-5197
	Darrell J. Panuch - Psychiatry	433-4406

	Yes	No
Do you/your child understand that you/your child have been asked to be in a research study?	—	—
Have you/your child read and received a copy of the attached Information Sheet?	—	—
Do you/your child understand the benefits and risks involved in taking part in this study?	—	—
Have you/your child had an opportunity to ask questions and discuss this study?	—	—
Do you/your child understand that you/your child are free to withdraw from the study at any time, without having to give a reason and without affecting your/your child's future medical care?	—	—
Has the issue of confidentiality been explained to you/your child, and do you/your child understand who will have access to your/your child's medical records?	—	—
Do you/your child want the investigator(s) to inform your/your child's family doctor that you/your child are participating in this research study?	—	—

Who explained this study to you/your child?

Signature of Research Subject _____

(Printed Name) _____

Signature of Parent/Guardian _____

(Printed Name) _____

Relationship to Subject _____

Signature of Witness _____ Date _____

Signature of Investigator or Designee _____

THE INFORMATION SHEET MUST BE ATTACHED TO THIS CONSENT FORM AND A COPY GIVEN TO THE RESEARCH SUBJECT