INHIBITORY CONTROL AND NEUROBIOCHEMICAL CHANGES IN CHILDREN WITH ATTENTION DEFICIT/ HYPERACTIVITY DISORDER (ADHD) AND CHILDREN WITH TRAUMATIC BRAIN INJURY (TBI)

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Kerstin Konrad

aus Essen

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CONTENTS

1. GENERAL INTRODUCTION

1.1 THE CLINICAL PICTURES: ATTENTION DEFICIT / HYPERACTIVITY DISORDER (ADHD) AND TRAUMATIC BRAIN INJURIES (TBI)

1.1.1 Children with ADHD and children with TBI - What do they have in common?

Brain injured children and children with attention deficit and hyperactivity disorder (ADHD)[1] often present similar behavioral profiles, characterized by deficits in attention, organization and problem solving abilities as well as fidgeting and poor affective control.

Phenomena commonly described after brain injuries are ”dysexecutive syndrome” (Baddeley & Wilson, 1988), ”environmental dependency syndrome” (Shallice, Burgess, Schon & Buxter, 1989), ”utilization behavior” (Lhermitte, 1983; Lhermitte, Pillon & Serdaru, 1986; Shallice et al., 1989), “organic personality change” (see DSM-IV) or “frontal lobe lobishness” (Stuss & Benson, 1986; Fuster, 1989). Although the different terms highlight different aspects of behavior, all syndromes have a degree of behavioral disinhibition in common. On the whole, it seems as if the behavior is controlled by external cues rather than internal information.

Hyperactive children are commonly described as under-controlled, impulsive and disinhibited. They blurt out answers in the classroom, cannot wait for their turn, shift from one activity to another and interrupt other children’s games. Again, these children are characterized by a deficit in response modulation and behavioral inhibition.

Response modulation and inhibition is of interest, since both are essential features of self-regulating behavior, empathy, planning, integration across space and time, delay of gratification etc. and therefore may have a large impact on children’s peer relations (Pettersen, 1991), school performance (Donders, 1994; Kaufmann, Fletcher & Levin, 1993) as well as on rehabilitation outcome (Parker, 1994; Ylvisaker, Szerkes & Hartwick, 1992).

In addition to the functional similarities between hyperactive and brain injured children both groups often respond in similar ways to the same pharmacological treatments, e.g., to methylphenidate or dextro-amphetamine (Solanto, 2000; Hornyak, 1997). These psychostimulants potentiate the action of dopamine and norepinephrine in the synapse by facilitating release, blocking re-uptake, and to a lesser extent, inhibiting the catabolic activity of monoamine oxidase (Solanto, 2000). Thus, it can be hypothesized that

[1] For better reading, in the following the terms “ADHD” and “hyperactive children” will be used as synonyms.

children with ADHD and children with TBI may suffer from similar changes in the dopaminergic and norepinephrinergic systems.

Neuroanatomically, the disinhibitory symptomatology has been most commonly associated with a frontal lobe dysfunction, which may be also present in both groups although in qualitatively different ways (Lezak, 1994).

Before attempting to find common underlying factors, both diseases are shortly described in the following sections.

1.1.2 ADHD - Prevalence

Attention deficit hyperactivity disorder (ADHD) is one of the most common behavioral disorders of childhood and adolescence (Taylor, 1995). According to American data the diagnosis is applicable to approximately 3 - 6% of school-age children (American Psychiatric Association (APA), 1994), with males being overrepresented by ratios ranging from 3:1 to 9:1.

In Germany, the epidemiological data are comparable, for example, in a recent study by Lauth and Lamberti (1997) it was shown that the prevalence rate of ADHD was 7,2% among children aged between 7 and 11 years.

ADHD encompasses the life span, affecting children from preschool to school age and continuing through adolescence into adulthood, albeit with age- and gender-related changes in its manifestations (e.g., Barkley, Fischer, Edelbrock & Smallish, 1990; Biederman et al., 1996).

The core behavioral symptoms of inattention, impulsiveness and hyperactivity cause significant impairment in family and peer relationships. Similarly affected is the ability to succeed in school during childhood and there is an increased risk of social isolation, serious driving accidents and additional psychopathology in adolescence and adulthood (e.g., Barkley et al., 1990; Biederman et al., 1996; Weiss & Hechtman, 1986; 1993).

1.1.3 Diagnosing ADHD according to the recent nosological frameworks: DSM-IV (APA, 1994) and ICD-10 (WHO, 1992)

On the basis of research demonstrating the functional similarity between hyperactivity and impulsivity and the functional dissimilarity between hyperactivity/ impulsivity and inattention (Lahey et al., 1988) DSM-IV delineated two types of symptoms:

inattention and hyperactivity/ impulsivity. Accordingly, two lists with nine symptoms each were introduced. The detailed diagnostic criteria are shown in Table 1.1.

Table 1.1 Diagnostic criteria for Attention-Deficit/ Hyperactivity Disorder.

A. Either (1) or (2):

(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) often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities
(b) often has difficulty sustaining attention in tasks or play activities
(c) often does not seem to listen when spoken to directly
(d) often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions)
(e) often has difficulty organizing tasks and activities
(f) often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)
(g) often loses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books, or tools)
(h) is often easily distracted by extraneous stimuli
(i) is often forgetful in daily activities

(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) often fidgets with hands or feet or squirms in seat
(b) often leaves seat in classroom or in other situations in which remaining seated is expected
(c) 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)
(d) often has difficulty playing or engaging in leisure activities quietly
(e) is often "on the go" or often acts as if "driven by a motor"
(f) often talks excessively

Impulsivity

(g) often blurts out answers before questions have been completed
(h) often has difficulty awaiting turn
(i) 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 Al and A2 are met for the past 6 months

314.00	**Attention-Deficit/Hyperactivity Disorder, Predominantly Inattentive Type:** if Criterion AI 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 AI is not met for the past 6 months

It is argued that the two symptom clusters (inattention versus hyperactivity/impulsivity) are distinct in terms of their etiology, clinical course, correlates, response to treatment and outcome (Lahey et al., 1994). The predominantly hyperactive-impulsive type actually seems to be a developmental precursor to the combined type (Barkley, 1997). In the field trials for ADHD in DSM-IV this hyperactive-impulsive type was chiefly found among preschool children (Applegate et al., 1995). In contrast, the combined type was far more heavily represented in school-aged children. Nearly the entire sample of the inattentive type was also found to be made up of school-aged children, whose attentional problems appear to have their onset even later than those that would eventually be associated with hyperactive-impulsive behavior (Applegate et al., 1995). Moreover, it appears that the predominantly inattentive type may have impairments in attention that are distinct from those found in the other two types (Barkley, 1997; Barkley, Grodzinsky, & DuPaul, 1992; Goodyear & Hynd, 1992; Hinshaw, 1994; Lahey & Carlson, 1992, for reviews). Research on the inattentive subtype suggests that symptoms of daydreaming, ”spacing out”, ”being in a fog”, ”being easily confused”, ”staring frequently”, and ”being lethargic, hypoactive, and passive” are more common (Barkley, DuPaul & McMurray, 1990; Lahey & Carlson, 1992). This type of ADHD has a deficit in speed of information processing, generally, and in focused or selective attention, specifically (Goodyear & Hynd, 1992; Lahey & Carlson, 1992).

Despite these empirical findings ICD-10 continued to require the presence of all three symptoms (hyperactivity, inattention and impulsivity) for a diagnosis of ADHD. As a consequence, the hyperkinetic disorder of ICD-10 should correspond closely to the DSM-IV combined type and is generally thought to define a more severely impaired subgroup of children with ADHD than DSM-IV (Schachar, 1991; Taylor, 1996). Nevertheless, both classification systems agree that the presence of pervasive symptoms is necessary for a diagnosis of ADHD.

1.1.4 TBI in childhood – Prevalence

Severe traumatic brain injury occurs in about 15.000 children annually in the USA (Di Scala, Lescohier, Barthel, & Li, 1991). Although precise epidemiological data are missing, it is estimated that each year 300.000 persons suffer from an accident with a brain injury in Germany. In a third of these cases a severe TBI is diagnosed. About 40% of the casualties are below 25 years of age and every 5th casualty is a child under 15 years of age. Clearly TBI is a major public health problem.

Due to advances in acute and emergency medicine as well as in neurosurgery, the survival rate of these patients has dramatically increased, however, the result of the decreased mortality is an increased number of young patients with significant physical and cognitive disabilities after a severe head injury.

Observation of differences in severity and mortality have led to the common misperception that children have generally better functional recovery than adults (Kennard Principle). This has not been supported by recent research. In fact, there is mounting evidence that children may have less favorable long-term functional outcomes than some adults, and that very young children are at greater risk of long-term impairment than older children (Capruso & Levin, 1992; Goldstein & Levin, 1985; Oddy, 1993).

1.1.5 Cognitive and behavioral consequences of TBI

It has been well established that TBI in children is often associated with a variety of cognitive and behavioral deficits, the extent of these being directly related to levels of injury severity (Dalby & Obrzut, 1991; Oddy, 1993; Telzrow, 1987). Severely injured children often continue to exhibit significant cognitive problems several years after injury, whereas mild TBI most often produces few (if any) clinically significant long-term cognitive sequelae (Fay et at., 1993; Fay et al., 1994).

Various cognitive deficits after relatively severe pediatric TBI have been described. With regard to psychometric intelligence, children with TBI often demonstrate greater and more persistent decrements in Performance IQ than in Verbal IQ (Chadwick, Rutter, Brown, Shaffer, & Traub, 1981; Chadwick, Rutter, Shaffer, & Shrout, 1981; Winogron, Knights, & Bawden, 1984). Deficits in memory and attention are among the most significant and pervasive cognitive sequelae of pediatric TBI (Bassett & Slater, 1990; Donders, 1993; Kaufman, Fletcher, Levin, Miner, & Ewing-Cobbs, 1993; Levin, Eisenberg,

Wigg, & Kobayashi, 1982). Furthermore, these children often display deficits on tasks that emphasize speed of performance, especially when a motor component is involved (Bawden, Knights & Winogron, 1985; Chadwick et al., 1981). Linguistic deficits are less pervasive, although persistent deficits in expressive language abilities and especially written expression may occur (Ewing-Cobbs, Levin, Eisenberg & Fletcher, 1987; Ewing-Cobbs, Miner, Fletcher & Levin, 1989; Jordan & Murdoch, 1990).

Because the cognitive sequelae that are associated with (especially severe) TBI can seriously interfere with the child's ability to cooperate with others and remember new information, it is not surprising that poor academic achievement and need for special education support are common (Cooley & Singer, 1991; Donders, 1994; Savage & Wolcott, 1994).

The cognitive sequelae of TBI can now be classified as a “cognitive disorder not otherwise specified” in DSM-IV. This represents an important improvement over previously used categories such as delirium or dementia, neither of which characterized accurately the nature and scope of cognitive impairment after TBI in children. Moreover, DSM-IV has proposed research criteria for postconcussional disorders.

The US National Pediatric Trauma Registry reported that 210 (73%) of 286 children with TBI who were discharged from a major trauma unit with multiple functional impairments also have behavioral difficulties (Di Scala et al., 1991).

In a German sample of 863 children, it was estimated that 40 - 100% suffered from expressive language, speech and communication problems and that as many as 80 - 100% suffered from behavioral disturbances and mental disorders after a brain injury (Mayer & Wiechers, 1993).

This agrees with American data which suggest that severe TBI in childhood is associated with an increase in psychiatric symptoms (Brown, Chadwick, Shaffer, Rutter, & Traub, 1981; Fletcher, Ewing-Cobbs, Miner, Levin, & Eisenberg, 1990; Knights et al., 1991; Papero, Prigatano, Snyder, & Johnson, 1993; Pettersen, 1991). Symptoms after TBI described in the literature include behavioral disinhibition, irritability, impaired interpersonal pragmatics, and/or deficient sensitivity to facial expression and contextual cues. As to cognitive problems, these psychiatric sequelae may sometimes only manifest themselves relatively late (sometimes years) after injury, when the child reaches a stage of development with different social and emotional demands (Oddy, 1993). Furthermore, behavioral sequelae may overlap with cognitive sequelae (Michaud, Rivara, Jaffe, Fay & Dailey, 1993). There is some controversy about the extent to which psychiatric problems

represent "true" sequelae of TBI or are simply pre-existing conditions. There is no evidence that premorbid behavioral or psychosocial factors play a major role in relatively severe pediatric TBI (Donders, 1994). However, some authors (e.g., Brown et al., 1981; Fletcher et al., 1990) have provided persuasive evidence that reports of psychiatric changes after mild TBI may be largely due to pre-existing difficulties in the vast majority of cases. Even in a carefully screened sample without premorbid deficits, there may be a subset of children with mild TBI that demonstrates behavior problems post injury that were simply not observed prior to injury (Asarnow, Satz, Light, Lewis & Neumann, 1991).

What exactly determines why some children with TBI develop psychiatric problems whereas others do not remains a matter of speculation. Injury severity clearly plays an important role, as children with severe injuries have been reported to exhibit more significant deficits and declines in behavioral adjustment, social competence, and general adaptation than children with mild to moderate injuries (Asarnow et al., 1991; Brown et al., 1981; Fletcher et al., 1990; Perrott, Taylor & Montes, 1991). At the same time, pre-injury child and family functioning play at least a moderating role. For example, child adjustment one year after injury appears to be better in families that are very cohesive and not overly controlling (Rivara et al., 1993).

1.1.6 Diagnosing ADHD after TBI

Among the secondary posttraumatic psychiatric sequelae after TBI, ADHD is the most common behavioral disorder (Gerring et al., 1998; Max et al., 1998). Since the age criterion (onset before age 7 years) is ignored in cases of TBI, one speaks about ”secondary ADHD”.

There have been two published prospective childhood psychiatric studies focusing on externalizing behavior disorders of TBI in which standardized instruments were used (Brown et al., 1981; Max et al., 1997). Brown et al. (1981) studied subjects over a 2-year follow-up period. They found that a new psychiatric disorder developed in 12 of 25 severe TBI subjects who had no psychiatric disorder prior to injury. Included in this group was an unclassifiable pattern of psychopathology which resembled the 'frontal lobe syndrome" in five of the severe TBI subjects. The disorder later evolved into a hyperkinetic syndrome in two subjects. This led the investigators to consider that the hyperkinetic syndrome following TBI may be related directly to brain damage.

Max et al. (1997) found that 4 of 13 severe TBI subjects had an ongoing, new ADHD at follow-up 2 years after TBI. Organic personality syndrome was comorbid in three of these subjects and had resolved approximately 1 year after TBI in the fourth subject. They also found that in their combined mild and moderate TBI group (n = 30), only one subject developed a new ADHD. This subject had a brief organic personality syndrome which resolved before the 3-month follow-up. Three other subjects within the group of 30 had their preinjury ADHD remain stable, while one improved markedly and no longer met criteria for ADHD and another child with preinjury undifferentiated attention deficit disorder also experienced resolution of the disorder.

Black et al. (1971) conducted a prospective psychiatric study without standardized instruments. The study population consisted of 105 children consecutively admitted for TBI. Most of these children had mild TBI. Approximately 80% of the children showed no posttraumatic behavioral changes. Among the children with changes, hyperactivity was already prevalent 3 months after the injury. The early onset of hyperactivity may be a clue that it was related directly to brain damage.

Furthermore, Gerring et al. (1998) found that children after TBI develop a secondary ADHD at a higher rate than expected in the general population (3 to 6%): At one year after injury, 28% of the participating children fulfilled DSM-III-R diagnostic criteria for ADHD (13 ADHD premorbid).

In addition to the above prospective TBI studies, one other psychiatric study estimated the frequency of postinjury ADHD (Max et al., 1997). Subjects were 50 consecutive patients referred to a pediatric speciality clinic for TBI. The most frequent current diagnosis was ADHD (n = 28; 56%), which included 10 subjects with ADHD prior to the injury.

To study prospectively the course of attention-deficit hyperactivity (ADH) symptomatology in children and adolescents after TBI, Max et al. (1998) repeated the psychiatric assessments 3, 6, 12, and 24 months after the TBI. It was hypothesized that ADHD symptomatology would be significantly related to severity of injury. They also tried to find a characteristic lesion or neuroimaging correlate of post-TBI change in ADHD symptomatology. In this study, Max et al. (1998) decided to analyze structural characteristics of the frontal lobe because this has been implicated in the etiology of ADHD (see also chapter 1.2.2) and not to focus on lesions per se because not all subjects had a brain lesion identified on the initial CT scan and because identifiable lesions, even on magnetic resonance imaging, may not reflect the full extent of parenchymal damage

(Berryhill, Lily & Levin, 1995). Negative correlations of change in ADHD symptoms and the bicaudate ratio were observed, but did not survive a correction for multiple tests. Thus, no neuroimaging correlate of post-TBI change in ADHD symptomatology was found. However, the results indicated that change in ADHD symptomatology in the first 2 years after TBI in children and adolescents was significantly related to severity of injury. Besides, overall ADHD symptomatology during the study was significantly related to a measure of family dysfunction when family psychiatric history, socioeconomic status, and severity of injury were controlled. The authors concluded that the presence of a positive ”dose-response”-relationship between severity of injury and change in ADHD symptoms, present from the 3-month assessment, was consistent with an effect directly related to brain damage.

In addition to ADHD, personality change after closed head injury may occur in children (APA, 1994). Commonly, as in adult neuropsychology, this disorder has been seen as a direct *organic* sequelae of TBI and has been labeled a “frontal lobe syndrome”, that includes disinhibition, lack of judgment or foresight, and moods that can range from apathy to euphoria (Gerring et al., 1998). The DSM-IV (APA, 1994) has introduced a diagnosis of ”personality change due to TBI” under those circumstances. It should be noted, however, that this would require a duration of symptoms of at least one year and that there must be conclusive evidence to suggest that the syndrome is a direct physiological consequence of the TBI. However, it is especially difficult to prove this latter point.

In their prospective study Brown et al. (1981) described 5 of the 31 severely injured children as having a “disinhibited state” with symptoms that included overtalkativeness, carelessness in personal hygiene, impulsiveness and outspokenness without regard for social convention. Brown described these children as resembling adults with frontal lobe syndromes due to brain injuries.

Interestingly, it has also been shown that children with ADHD are expected to be overly represented in a sample of children who have suffered from a traumatic brain injury, since hyperactivity, impulsivity and inattention place children at increased risk for engagement in dangerous activities (Barkley et al., 1993; Bijur et al., 1988). Therefore, the premorbid rate of ADHD must be taken into account when diagnosing behavioral disorders after TBI.

In fact, one of the *DSM-III-R* criteria for ADHD was “often engages in physically dangerous activities without considering possible consequences (not for the purpose of

thrillseeking), e.g., runs into street without looking" (APA, 1987). Hence, one would expect children with ADHD to be overly represented in a sample of children who suffer a traumatic brain injury, a fact which was demonstrated by Gerring et al. (1998), reporting a premorbid prevalence rate of ADHD of 20% in his above cited study.

A further study was conducted by DiScala et al. (1998). They compared children with preinjury attention deficit hyperactivity disorder (ADHD) to those with no preinjury conditions with respect to the frequency of injuries requiring hospital admission. They examined a total of 240 ADHD patients and 21,902 patients without a premorbid ADHD (from 5 to 14 years of age). They found that compared to the normal children, children with ADHD were more likely to be injured as pedestrians (27.5% vs 18.3%) or bicyclists (17.1% vs 13.8%), and to inflict injury on themselves (1.3% vs 0.1%). They were more likely to sustain injuries to multiple body regions (57.1% vs 43%), to sustain head injuries (53% vs 41%), and to be severely injured as measured by the Injury Severity Score (12.5% vs 5.4%) and the Glasgow Coma Scale (GCS) (7.5% vs 3.4%). In both groups, 40% had surgery, but the ADHD children were admitted more frequently to the intensive care unit (37.1% vs 24.1%). The injury led to disability in 53% of the children with ADHD vs 48% of the normal children. These figures demonstrate that ADHD is a high-risk group for any forms of accidents.

1.1.7 Summary

A number of similarities between children with ADHD and brain injured children were described in chapter 1.1, the most obvious being the deficit in behavioral inhibition. However, the functional overlap between the disorders is confounded by a higher risk of ADHD children being involved in severe accidents (including TBIs). Besides, recent studies suggest that TBI children have a three to five times higher risk of developing ADHD. Another mental disorder associated with behavioral disinhibition after TBI is the diagnosis of organic personality change. However, it remains an unanswered question as to which children develop a disinhibitory symptomatology after a TBI. Although the frontal lobe, striatum, and thalamus are regarded as neuroanatomical structures involved in personality change or ADHD symptoms after TBI (Gerring et al., 1998; Mega & Cummings, 1994) no neuroanatomical correlates have yet been identified. A more detailed view on the relationship between brain mechanisms and ADHD will be presented in chapter 1.2.

1.2 BRAIN MECHANISMS IN ADHD

1.2.1 ADHD - The historical view on the association with brain injury

Historically, ADHD is a rather old and well known behavioral disorder, as the famous German tale ”The fidgeting Phil” demonstrates, which was written in 1848 by the German neurologist Heinrich Hofmann. Besides, research on this disorder has a long tradition and history. A summary the history of ADHD research will follow, since in the very early stages of research the link between ADHD symptoms and brain injuries was very popular. Although the concept of minimal brain damage in children with ADHD has lost more than gained acceptance over the last years the historical perspective demonstrates well the similarities between ADHD children and brain damaged children. The main parts of the following section refer to Barkley’s (1990) as well as to Schachar’s (1986) historical reviews.

In his historical review, Barkley (1990) summarized four periods of ADHD research.

First period: 1900 to 1960: ”age of the brain damaged child”

This early period of ADHD research between 1900 to 1960 was called the ”age of the brain damaged child” by Barkley. The few papers about ADHD at that time were clearly medical in nature and often described the cognitive and behavioral late effects of various central nervous system (CNS) injuries, such as trauma and infections. One of the most important early researchers was George Still. Still (1902) described 20 children in his clinical practice who were often aggressive, resistant to discipline and showed little ”inhibitory volition”. Most of the children were impaired in attention and quite overactive. Following the theorizing of Williams James (1890), Still (1902) hypothesized that deficits in inhibitory volition, moral control and sustained attention were causally related to each other and to the same underlying neurological deficiency. He cautiously speculated on the possibility of either a decreased threshold for inhibition of responding to stimuli or a cortical disconnection syndrome (that might be due to neuronal cell modification) in which intellect was dissociated from will or social conduct. ADHD was seen as little affected by social circumstances, but as a biological, often hereditary, predisposition to defects in the regulation of behavior. Problematic in this early view was the implicit foundation on a social darwinist perspective of childhood behavioral disorders that was highly pessimistic about prognosis and which viewed most or all abnormal behavioral disorders as

biologically determined – a view which was criticized sharply by Schachar (1986) in his historical review.

A further important influence on ADHD research in North America was the outbreak of an encephalitis epidemic in 1917-1918, when clinicians were presented with a number of children who survived this brain infection yet were left with significant behavioral and cognitive sequelae (Cantwell, 1981; Kessler, 1980; Stewart, 1970). Numerous papers reported on these problems: children were described as being impaired in attention, regulation of activity and impulse control as well as in other cognitive abilities (including memory). Besides they were often noted to be socially disruptive (Ebaugh, 1923; Hohman, 1922; Strecker & Ebaugh, 1924). The disorder was referred to as ”postencephalitic behavior disorder”, and was clearly the result of brain damage. What was especially interesting from a therapeutic view was the fact that despite a rather pessimistic view of the prognosis of these children, some facilities reported significant success in their treatment, using simple behavior modification programs and increased supervision (Bender, 1942; Bond & Appel, 1931).

The association of a brain disease with behavioral pathology apparently led early investigators to study other potential causes of brain injury in children and their behavioral manifestations, e.g., lead toxicities (Byers & Lord, 1943), epilepsy and head injury (Blau, 1936; Werner & Strauss, 1941). Therefore, it was not surprising that according to the early descriptions, many of these children were also mentally retarded or more seriously behaviorally disordered than are children today who are described as having ADHD.

Notable during this era was also the recognition of the striking similarity between the symptoms exhibited by hyperactive children and the behavioral sequelae of frontal lobe lesions in primates (Blau, 1936; Levin, 1938). Frontal lobe ablation studies of monkeys had been performed since 1876 (Ferrier, 1878) and were known to result in excessive restlessness, poor ability to sustain interest in activities, aimless wandering, and excessive appetite, among other behavioral changes. Several investigators, such as Levin (1938), used these similarities to postulate that severe restlessness in children was most likely the result of pathological defects in the forebrain structures, although gross evidence of such defects was not always apparent in many of these children. Later investigators (Chelune, Ferguson, Koon & Dickey, 1986; Lou, Henriksen & Bruhn, 1984; Lou, Henriksen, Bruhn, Bomer & Nielsen, 1989; Mattes, 1980) returned to this notion, but with greater evidence to substantiate their claims. Milder forms of hyperactivity, in contrast, were attributed in this

era to psychological causes, such as poor child-rearing practices or delinquent family environments.

Since most of the hospitalized children had actually suffered from some kind of brain damage, this led professionals to believe that behavioral patterns were a reliable indicator of an underlying CNS etiology or damage, even in cases where evidence of such an association was lacking. In fact, Strauss and Lehtinen (1947) argued that the psychological disturbance was in fact evidence of brain injury as an etiological factor. This argument evolved later into the concept of ”minimal brain damage” or minimal brain dysfunction (MBD). Few early voices, such as Childers (1935), raised serious questions about the notion of brain damage in these children where no historical documentation of damage existed. Substantial recommendations for educating these brain-damaged children were made in the classic text by Strauss and Lehtinen (1947); these included placing them in smaller, more carefully regulated classrooms and reducing the amount of distracting stimulation in the environment.

Another significant series of papers on treatment of these children appeared in 1937 to 1941; these were to mark the beginnings of medication therapy for behaviorally disordered children in particular, as well as the origins of the field of child psychopharmacology in general (Bradley, 1937; Bradley & Bowen, 1940; Molitch & Eccles, 1937). These papers reported on the efficacy of amphetamines in reducing disruptive behavior and improving academic performance of behaviorally disordered children. Later studies also confirmed such a positive drug response in half or more of hyperactive hospitalized children (Laufer, Denhoff, & Solomons, 1957). As a result, by the 1970s, stimulant medication was to become the treatment of choice for the characteristics of ADHD.

In the 1950s, a number of investigations on the neurological mechanisms underlying these behavioral symptoms were conducted, the most famous of which was the study by Laufer et al. (1957). This research group referred to ADHD children as having “hyperkinetic impulse disorder” and reasoned that the CNS deficit occurred in the thalamic area. Here, poor filtering of stimulation was thought to occur, allowing an excess of stimulation to reach the brain. Their evidence was based upon a study of the effects of the photo-Metrozol method, in which the drug Metrozol was administered while flashes of light were presented to the child. The amount of drug required to induce a muscle jerk of the forearms, along with a spike-wave pattern in the electroencephalogram, served as the measure of interest. Laufer et al. found that hyperactive inpatient children required less

Metrozol than nonhyperactive inpatient children to induce this pattern of response. This suggested that hyperactive children had a lower threshold for stimulation in the thalamic area. The study was never replicated, and it is unlikely that such research would pass the standards of ethical conduct required by today's institutional review boards on research with human subjects.

Others at the time also conjectured that an imbalance between cortical and subcortical areas existed, such that there was diminished control of subcortical areas responsible for sensory filtering, which permitted excess stimulation to reach the cortex (Knobel, Wolman & Mason, 1959).

By the end of this era it seemed well accepted that hyperactivity was a brain damage syndrome, even where evidence of damage was lacking. The disorder was thought to be best treated through severely austere minimal stimulation educational classrooms or residential centers. Its prognosis was considered fair to poor. The possibility that a relatively new class of medications, the stimulants, might hold promise for its treatment was only beginning to be appreciated.

Second period: 1960 to 1969: ”the golden age of hyperactivity”

This period is called by Barkley ”the golden age of hyperactivity”. In the late 1950s and early 1960s, critical reviews began to question the concept of a unitary syndrome of brain damage in children. They also pointed out the logical fallacy inherent in the assumption that if brain damage resulted in some of these behavioral symptoms, these symptoms could be pathognomonic of brain damage without any other corroborating evidence of CNS lesions. Chief among these critical reviews were those of Birch (1964), Herbert (1964), and Rapin (1964), who all questioned the validity of applying the concept of “minimal brain damage” (MBD) to children who had only equivocal signs of neurological involvement, not necessarily damage. Apparently as a result of this controversy, a change in terms followed, with MBD being substituted. However, the concept of MBD eventually also died a slow death as it became recognized as vague, overinclusive, of little or no prescriptive value, and without much neurological evidence (Kirk, 1963). More specific labels applying to somewhat more circumscribed cognitive, learning, and behavioral disorders, such as ”dyslexia”, ”language disorders”, ”learning disabilities”, and ”hyperactivity” were introduced in the following years. These labels were based on the observable and verifiable deficits of the children they described, rather than on some underlying unobservable etiological mechanism in the brain.

As dissatisfaction with the term MBD was occurring, concurrently the concept of a "hyperactive child syndrome" arose, described in the classic papers by Laufer and Denhoff (1957) and Stella Chess (1960), and in other papers of this era (Burks, 1960; Ounsted, 1955; Prechti & Stemmer, 1962). Chess defined hyperactivity as follows: "The hyperactive child is one who carries out activities at a higher than normal rate of speed than the average child, or who is constantly in motion, or both" (p. 2379). The official catalogue of diagnostic nomenclature at the time, the second edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-II; APA, 1968), followed suit in creating the Hyperkinetic Reaction of Childhood Disorder. However, other than briefly describing the excessive activity level of these children, this diagnostic manual provided few useful details for reliable clinical diagnosis.

Unlike Still (1902), Chess and others writing in this era stressed the relatively benign nature of ADHD symptoms and claimed that in most cases the disorder was resolved by puberty (Laufer & Denhoff, 1957; Solomons, 1965).

It was perhaps during this period, or even a little earlier, that the perspective on hyperactivity taken in North America began to diverge from that taken in Europe, particularly in Great Britain. In North America, hyperactivity came to be seen as a behavioral syndrome characterized chiefly by greater-than-normal levels of activity, was viewed as a relatively common disturbance of childhood, was not necessarily associated with demonstrable brain pathology, and was considered more of an extreme degree in the normal variation of temperament in children. In Great Britain, the narrower view that hyperactivity or hyperkinesis was an extreme state of excessive activity of almost driven quality, was highly uncommon, and usually occurred in conjunction with other signs of brain damage (such as epilepsy, hemiplegias, or retardation) or a clearer history of brain insult (such as trauma or infection) continued into the 1970s (Taylor, 1988). The divergence in views led to large discrepancies between North American and European investigators in their estimations of the prevalence of the disorder, their diagnostic criteria, and their preferred treatment modalities.

The third period: 1970 to 1979: "the ascendance of attention deficits"

The following period was called "the ascendance of attention deficits" by Barkley. By the early 1970s, the defining features of the hyperactive or hyperkinetic child syndrome had been broadened to include what were previously felt to be only associated characteristics, including impulsivity, short attention span, low frustration tolerance, distractibility, and aggressiveness (Marwit & Stennet, 1972; Safer & Allen, 1976).

The concept of MBD faded from clinical and scientific usage by the end of this decade. In cases of well-established cerebral damage, the behavioral sequelae were not uniform across cases, and hyperactivity was seen in only a minority. Hence, contrary to 25 years of theorizing up to this point, hyperactivity was not a common sequel of brain damage; truly brain-damaged children did not display a uniform pattern of behavioral deficits; and children with hyperactivity rarely had substantiated evidence of neurological damage (Rutter, 1989).

At this time a disenchantment with the exclusive focus on hyperactivity as the sine qua non of this disorder developed (Werry & Sprague, 1970). It was argued that deficits in sustained attention and impulse control were more likely to account for the difficulties seen in these children than hyperactivity. These were also seen as the major areas of impact of the stimulant medications used to treat the disorder.

Douglas' (1972) extensive and thorough battery of objective measures of various behavioral and cognitive domains allowed to rule in or out various characteristics felt to be typical for these children in earlier clinical and scientific lore. For instance, she found that hyperactive children were not necessarily more reading- or learning-disabled, did not perseverate on concept learning tasks, did not manifest auditory or right-left discrimination problems, and had no difficulties with short-term memory. Most importantly, Douglas (1972) demonstrated that hyperactive children were not more distractible than normal children and that the sustained attention problems could emerge in conditions where no significant distractions existed. She also remarked on the extreme degree of variability demonstrated during task performances by these children - a characteristic that was later advanced as one of the defining features of the disorder.

Finally, of substantial significance were the observations of Douglas' colleague, Gabrielle Weiss, from her follow-up studies (see Weiss & Hechtman, 1986) that while the hyperactivity of these children often diminished by adolescence, their problems with poor sustained attention and impulsivity persisted.

In 1980 with the publication of DSM-III (APA, 1980), the disorder was renamed in Attention Deficit Disorder (ADD). In this revised official taxonomy, deficits in sustained attention and impulse control were now formally recognized as of greater significance in the diagnosis than hyperactivity. The shift to attention deficits rather than hyperactivity as the major difficulty of these children was useful, at least for a time, because of the growing evidence that hyperactivity was not specific to this particular condition, but could also be noted in other psychiatric disorders (e.g., anxiety, mania, autism.). There was no clear

delineation between normal and abnormal levels of activity, activity was in fact a multidimensional construct, and the symptoms of hyperactivity were quite situational in nature in many children (Rutter, 1989). But this approach only corrected the problem of definition for less than a decade before these same concerns began to be raised about the construct of attention (e.g., multidimensional, situationally, variable).

The 1970s were noteworthy for an explosion in the number of research studies conducted on the psychophysiology of hyperactivity in children. Numerous studies were published measuring galvanic skin response, heart rate acceleration or deceleration, various parameters of EEG, etc. Although most of the studies were methodologically flawed and often contradictory in their findings, the global outcome of this research was that hyperactive children showed a sluggish or underreactive electrophysiological response to stimulation. This laid to rest the belief in an overstimulated cerebral cortex as the cause of the symptoms in hyperactive children, but did little to suggest a specific neurophysiological mechanism for this underactivity.

The fourth period: 1980 to 1989: "age of diagnostic criteria and the waning of attention deficits"

This period is called the "age of diagnostic criteria and the waning of attention deficits" by Barkley, since this decade became notable for its emphasis on attempts to develop more specific diagnostic criteria. Experts (e.g., Rutter, 1983; Quay, 1987) in the field now called upon their colleagues to demonstrate that the symptoms of ADHD could distinguish it from other childhood psychiatric disorders – a crucial test for the validity of a diagnostic entity - rather than continuing to simply demonstrate that ADHD children differed from normal populations. The most exciting development in this period was to abandon the attention deficit model and to see ADHD as a motivation deficit disorder. Barkley summarized four reasons and sources for this development: "(1) its greater explanatory value in accounting for the more recent research findings on situational variability in attention in ADHD; (2) its consistency with neuroanatomical studies suggesting decreased activation of brain reward centers and their cortical-limbic regulating circuits (Lou, Henriksen & Bruhn, 1984; Lou et al., 1989) (3) its consistency with studies of the functions of dopamine pathways in regulating locomotor behavior and incentive or operant learning (Beninger, 1989); and (4) its greater prescriptive power in suggesting potential treatments for the ADHD symptoms" (Barkley, 1990, p.27).

1.2.2 The recent view on brain mechanisms in ADHD

Due to advances in structural and functional imaging techniques the understanding of developmental neuropsychiatric disorders has increased during the last years. However, knowledge of human brain development and normal variability in the structure and function of the developing brain across childhood is essential for the interpretation of differences associated with psychopathology (Tannock, 1998).

In ADHD research, the most commonly used techniques that focus on brain structure and anatomy include computerized transaxial tomography (CTT) and magnetic resonance imaging (MRI). Functional/dynamic techniques used to study brain metabolism and regional change in brain activity include position emission tomography (PET), single photon emission computerized tomography (SPECT), quantitative electrophysiology (QEEG) and event-related potentials (ERP) and functional magnetic resonance imaging (fMRI). The following section mainly refers to Tannock's (1998) review on the advances in neurobiological research as well as on the special issue on ADHD in Behavioral Brain Research (1998). Major findings of morphometric imaging studies and of SPECT, PET and one fMRI study will be reported.

Recent MRI studies suggest localized abnormalities in several brain regions, such as the prefrontal cortex, the basal ganglia and the corpus callosum in children with ADHD. For example, all three studies which have examined anterior frontal regions reported a smaller right prefrontal cortex (Castellanos et al., 1994; Filipek et al., 1997; Hynd et al., 1990) in ADHD. Four of the six studies that included basal ganglia measures reported differences in the caudate volumes with a corresponding loss of or reversal of the asymmetry found in normal controls, although there were disagreements about the normal pattern of asymmetry and the specific pattern of volumetric differences associated with ADHD (Castellanos et al., 1994; Castellanos, Giedd, Marsh et al., 1996; Filipek et al., 1997; Hynd et al., 1993). Moreover, a smaller globus pallidus in children with ADHD were reported in all four studies imaging this structure (Aylward et al., 1996; Castellanos, Giedd, Marsh et al., 1996; Castellanos, Giedd, Hamburger et al., 1996; Singer et al., 1993). By contrast, none of the three studies including volumetric and symmetry measures of the putamen found differences between ADHD and normal peers (Aylward et al., 1996; Castellanos, Giedd, Marsh et al., 1996; Castellanos, Giedd, Hamburger et al., 1996). Decreases in the corpus callosum have been observed in five of the six studies in which it was evaluated, although once again the studies provide conflicting information regarding

regional differences. For example, the posterior “splenium” region and the genu, rostrum, and rostral body in the anterior region have all been reported to be both smaller and similar in ADHD compared to normally developing children (Baumgardner et al., 1996; Castellanos, Giedd, Marsh et al., 1996; Giedd et al., 1994; Hynd et al., 1991; Semrud-Clikeman et al., 1994). Also, a smaller total cerebral volume and smaller cerebellum have been reported in children with ADHD (Castellanos, Giedd, Marsh et al., 1996). According to Giedd et al. (1996), anatomical measures may be able to discriminate between ADHD and normal peers. Specifically, three anatomical measures (right globus pallidus volume, caudate symmetry and left cerebellum volume) correctly classified group membership for 87% of the subjects with ADHD and 65% of the control subjects. Casey et al. (1997) found that decrements on inhibitory task performance correlated with those anatomical measures of fronto-striatal circuitry observed to be abnormal in children with ADHD (i.e. prefrontal cortex, caudate, globus pallidus, but not the putamen).

Many of the morphometric studies of ADHD suggest localized hemispheric structural anomalies that are concordant with theoretical models of abnormal frontal-striatal function in ADHD (e.g., Barkley, 1997; Benson, 1991; Heilman, Voeller & Nadeau, 1991; Mattes, 1980; Voeller, 1991) and with attentional network hypotheses (e.g., Mesulam, 1990; Morecraft, Geula, & Mesulam, 1993; Posner & Raichle, 1994). Also, the volumetric differences in the cerebellum as well as in the basal ganglia are interesting given the recent findings that both brain regions have neuronal links with the prefrontal cortex (Middleton & Strick, 1994). These connections provide part of the involvement of these subcortical nuclei in higher-order cognitive processes, such as working memory, rule-based learning, and planning (e.g., Middleton & Strick, 1994).

A more detailed examination of the data underscores marked and nontrivial inconsistencies in findings for normal controls as well as for the ADHD groups (e.g., the pattern of asymmetry of the caudate volume). In part, the discrepant findings may be due to differences in subject selection in terms of age groups, ratio of males to females, and comorbid diagnoses (all in relatively small samples), the limited data on neuropsychological characteristics or handedness, as well as inadequate matching of the subject and comparison groups for these variables. The inconsistencies are also attributable to differences in the MRI methods and image analysis, including scanning parameters, the approach to analysis, segmentation algorithms, and accuracy in anatomic identification.

More recently, functional imaging studies, as PET studies have demonstrated alterations in frontal lobe metabolism in ADHD. One study of adults with childhood-onset

ADHD, who were also parents of children with ADHD, revealed widespread and bilateral reduction in glucose metabolism that was most pronounced in the premotor cortex and superior frontal cortex, but also occurred in some subcortical structures, such as the striatum and thalamus (Zametkin et al., 1990). These are regions that have been shown to be involved in the control of motor activity and attention (e.g., Mesulam, 1990; Wise, 1985). A subsequent study of cerebral glucose metabolism in adolescents with ADHD found decreased metabolism in frontal, temporal, thalamic, and hippocampal areas, but the overall reductions in metabolism were minimal and nonsignificant (Zametkin et al., 1993). Of interest are indications that females with ADHD tend to show greater brain metabolism abnormalities than males (Ernst et al., 1994; Zametkin et al., 1993). These findings suggest that gender and age must be considered in understanding the pathophysiology of ADHD (Ernst et al., 1994). The effects of stimulants on cerebral glucose metabolism are unclear. One study of acute effects demonstrated widespread changes, both increases and decreases in metabolism (Matochik et al., 1994), whereas a subsequent study of chronic administration of methylphenidate or dextroamphetamine found that neither medication changed brain metabolism, despite of marked behavioral improvements (Matochik et al., 1994). In contrast, using xenon emission tomography, Lou et al. (1984; 1989; 1990) found decreased blood flow to the frontal lobes in ADHD children, which increased after the children received methylphenidate. In the second report (1989), these authors emphasized the basal ganglia as the locus of reduced blood flow in ADHD. However, the findings must be interpreted with caution, given several methodological limitations (small sample, inclusion of subjects with developmental dysphasia and mental retardation).

Finally, the first published study using the I-123 IMP SPECT technique with children with ADHD revealed greater overall uptake asymmetry, with less activity in the left frontal and left parietal regions, but no difference in uptake asymmetry in temporal regions (Sieg, Gaffney, Preston & Hellings, 1995). Noting that the frontal regions are among the last regions of the brain to become myelinated (e.g., Yakovlev & Lecours, 1967), Sieg et al. (1995) speculated that both PET and SPECT findings may reflect maturational lags of the central nervous system resulting from delayed myelinization. Also, there is one preliminary report of a small-scale fMRI study of functional neuroactivation during inhibitory control (using a visual stop signal paradigm) in seven adolescents with ADHD and nine normal peers (Rubia et al., 1997). Findings indicated reduced brain activation in regions in the right hemisphere (anterior cingulate, pre- and postcentral gyrus, inferior

gyrus, posterior parasagittal and extrastriate cortex, posterior parietal cortex), but increased activation in subcortical areas (right insula and left caudate).

1.2.3 Summary

Although historically ADHD has been associated with brain damage for a long time, the concept of a ”minimal” structural damage was not supported by later empirical findings. However, findings from new neuroimaging studies have shown that the fronto-striatal networks are involved in the biology of ADHD. Since years, the role of the frontal cortex has been repeatedly discussed in the history of neuropsychology. For example, already Burdach (1819) called the frontal lobe the “special workshop of the thinking process”. More recent neuropsychological research has linked frontal lobe functions to executive or supervisory functions (e.g., Stuss & Benson, 1984; Stuss, Shallice, Alexander & Picton, 1995). This will be discussed in detail in the following chapter.

1.3 FRONTAL LOBE AND EXECUTIVE FUNCTIONS

The importance of the frontal lobes for human brain activity is reflected in their neuroanatomy. The human frontal lobe is considerably different from that of other animals. Its size in humans, usually estimated at between 24 and 33% of the total cortical surface (Goldman-Rakic, 1984), is far larger than that of any of the other apes. Phylogenetically, the human frontal lobe is the latest area to develop, reflecting its unique status in the evolutionary ladder, and also ontogenetically, as already mentioned, it is one of the last areas of the brain to reach full maturity (Yakovlev & Lecours, 1967; Luria, 1973).

The associative cortex of the frontal lobes, the prefrontal cortex, has been identified as the primary locus of executive functions, especially of behavioral inhibition (Fuster, 1989; 1986; Luria, 1973). The prefrontal cortex is structurally defined as the part of the neocortex that receives projections from the mediodorsal nucleus of the thalamus. It is a functionally heterogeneous area. Much of the evidence regarding the functions of the prefrontal cortex comes from comparative research involving frontal lesions and from human research involving individual cases of brain damage (Fuster, 1989).

Welsh and Pennington (1988) defined executive function ”... as the ability to maintain an appropriate problem-solving set for attainment of a future goal (Bianchi, 1922; Luria, 1966). This set can involve one or more of the following: (1) an intention to inhibit a

response or to defer it to a later more appropriate time, (2) a strategic plan of action sequences, and (3) a mental representation of the task, including the relevant stimulus information encoded into memory and the desired future goal state. In cognitive psychology, the concept of executive function is closely related to the notion of a limited-capacity central processing system" (pp. 201-202).

So the domain of executive function is distinct from cognitive domains, such as sensation, perception, and many aspects of language and memory. It overlaps with domains, such as attention, reasoning and problem-solving, although not perfectly. Typical lists of executive functions include set-shifting and set maintenance, interference control, planning, and working memory (Pennington & Ozonoff, 1996; Rabbitt, 1998). A central idea in the concept of executive function is context-specific action selection, especially in the context of strongly-competing, but context-inappropriate responses. Another central idea is maximal constraint satisfaction in action selection, which requires the integration of constraints from a variety of other domains, such as perception, affect and motivation. Hence, much complex behavior and much social behavior requires executive functions.

However, the definition of executive functions in neuropsychological and cognitive psychology is provisional and under-specified. The term also carries some implicit meaning. In cognitive psychology, executive processes are a kind of residual, the part of cognition that logically must occur after perception before action. In neuropsychology, an implicit meaning is essentially tasks that patients with frontal lesions do badly on. This definition by localization is, of course problematic, since not all executive functions are mediated by the frontal lobes and not all tasks impaired by frontal lesions are executive (Pennington & Ozonoff, 1996).

Recently, Barkley (1997) assumed a new model of executive functions based on the research of ADHD. He distinguishes three forms of response inhibition: (1) inhibiting prepotent responses, (2) stopping an on-going-response and (3) interference control. Barkley argues that ADHD involves a pervasive deficit in all forms of response inhibition. According to Barkley, this deficit leads to secondary impairments in four executive functions as working memory, internalisation of speech, self-regulation of affect and reconstitution.

1.3.1 Executive dysfunctions in children with ADHD

The hypothesis of an executive function deficit in ADHD has been advanced by several researchers (Gualtieri & Hicks, 1978; Mattes, 1980; Pontius, 1973; Rosenthal & Allen, 1978; Stamm & Kreder, 1979; Zametkin & Rapoport, 1986).

Pennington and Ozonoff (1996) summarized 18 studies in their review on ”executive functions and developmental psychopathology”. Fifteen of 18 studies found significant differences between ADHD subjects and controls on one or more executive function measures, as on the Trail Making Test, the Tower-of-Hanoi or the Stroop-Task. Average effect sizes (mean d) ranged from 0.27 for letter fluency tasks to 1.08 for the Tower-of-Hanoi. The Tower-of-Hanoi is a problem solving task in which beads on three vertical rods have to be rearranged to match a model. Verbal tasks did not appear to be very sensitive to ADHD. Besides the Tower-of-Hanoi, measures which were especially sensitive to ADHD were the Stroop Test, the Matching Familiar Figure Task (MFFT) errors, and the Trail making Test Part B whereas the Wisconsin Card Sorting Test (WCST) was less consistently impaired. The WCST is a classic measure of flexibility in problem solving that involves shifting response strategy by sorting cards according to changes in the salient dimension (i.e. color, shape, number). Clearer measures of motor inhibition (Go-No-Go, Stopping, Anti-Saccade, Conflict Motor Task) consistently found group differences with poorer performance in ADHD children compared to normal controls.

It was assumed that poor response inhibition may be the major deficit in children with ADHD. Unfortunately, the concept of response inhibition has no universally accepted definition (Barkley, 1994; 1996; Sonuga- Barke, 1995). As a result, it has been operationalized in a variety of ways. These measures include, for example the MFFT (DuPaul, Anastopoulos, Shelton, Guevremont & Metevia, 1992; Weyandt & Grant, 1994), the Continuous Performance Task (CPT, Barkley, Grodzinsky & DuPaul, 1992; Corkum & Siegel, 1993; Halperin et al., 1994), the Go-/No-Go-Task (Iaboni, Douglas & Baker, 1995; Shue & Douglas, 1992; Milich et al., 1994), Delayed Response Tasks (Daughtery & Quay, 1991; Mc Clure & Gordon, 1984; Solanto, 1990) or the WCST (for a review see Barkley et al., 1992). These measures, however, have been criticized for their poor construct validity and have been considered as too global (Schachar & Logan, 1990; Halperin et al., 1994). Performance on these measures may be influenced by many factors other than response inhibition, such as IQ. The major criticism levelled at these tasks is their failure to clarify the mechanisms underlying impaired response inhibition (Milich et al., 1994; Schachar & Logan, 1990). These criticisms do not apply to the Stop Task (Logan & Cowan, 1984;

Logan, Cowan, & Davis, 1984). This task is purported to measure the ability to interrupt an ongoing response (the Stop Signal task and its underlying mathematical model of response inhibition will be explained in more detail in chapter 2.7.). Several studies have supported the reliability and validity of the stop task as a measure of response inhibition (Kindlon, Mezzacappa, & Earls, 1995; Tannock, Schachar, Carr, Chajczyk, & Logan, 1989).

Logan and his colleagues have demonstrated that children with ADHD and especially children with pervasive ADHD symptoms compared to children with a situational symptomatology (symptoms occur only at home or only at school) showed a deficit in inhibitory control measured with the Stop Signal Task (Schachar, Logan, Wachsmuth & Chajczyk, 1988; Chee et al., 1989; Schachar & Logan, 1990; Schachar, Tannock, Marriott & Logan, 1995). Tannock, Schachar, Carr, Chajczyk and Logan (1989) as well as Tannock, Schachar and Logan (1995) also examined the influence of methylphenidate on stopping and found that ADHD children showed an improved response inhibition on stimulant medication.

In a recent meta-analysis, Osterlaan, Logan and Sergeant (1998) reviewed eight studies in which response inhibition was assessed with the so-called Stop Task in five groups of children, children with Attention Deficit/Hyperactivity Disorder (AD/HD), children with Conduct Disorder (CD), children with AD/HD + CD, children with anxiety disorders, and control children. A total of 456 children participated in these 8 studies. All children were in the age range between 6 and 12 years. Consistent and robust evidence was found for a response inhibition deficit in AD/HD. However, response inhibition deficits did not distinguish children with AD/HD from children with CD, nor from children with comorbid AD/HD + CD.

However, the primacy of the response inhibition deficit in ADHD has been called into question (e.g., Sonuga-Barke, 1995). That is, the possibility has been raised that the impairment in response inhibition in children with ADHD is, in fact, only one aspect of a more general dysfunction. It has been suggested that poor response inhibition originates from a disinclination to invest effort, or stated differently, reflects a motivational deficit (Osterlaan & Sergeant, 1988). Especially European researchers have argued that the inhibition deficit in ADHD is dependent upon the state of the subject and the allocation of energy to the tasks at hand (Sergeant, 2000). Sergeant stated a cognitive-energetic model which explains the response inhibition deficit in ADHD with inadequate activation of the actual inhibitory mechanism.

1.3.2 Executive dysfunctions in children with TBI

The frontal lobes are vulnerable to focal damage after closed head injury (Mendelsohn et al., 1992). Magnetic resonance imaging findings in children sustaining severe closed head injuries disclosed focal lesions restricted to or primarily involving the frontal lobes in 40% of the sample (Levin et al., 1993). Gray matter lesions were seen most frequently in orbitofrontal and dorsolateral areas; frontal white matter lesions were also commonly visualized (Levin et al., 1993). Given the frequent injury to frontal regions after TBI, the investigation of executive function deficits is critically important to the understanding of posttraumatic cognitive and behavioral changes. However, Goldberg and Bilder (1987) have noted that even in absence of focal frontal contusions *any* diffuse brain dysfunction can disrupt what we consider to be executive functions before other abilities.

Surprisingly, there are only few studies examining directly executive functions in children with TBI. Levin and coworkers (1991) performed a study on metacognition in brain injured children. Metacognition, which refers to the knowledge of one's own cognitive abilities, is an exemplar of the category of self-regulation. By monitoring the semantic features common to several words on a list, children can enhance their recall by clustering items from the same category (e.g., recalling all the fruits, then the vegetables). Use of the semantic clustering strategy implies verbal regulation and monitoring prior to recall. Levin and coworkers (1991) studied use of semantic clustering in 52 normal children and adolescents by administering the children's version of the California Verbal Learning Test (Delis et al., 1986), which consisted of 15 words representing three categories of items (e.g., fruits). Levin and colleagues (1991) found an interaction of age with gender: The increased semantic clustering after age 7-8 years was exhibited primarily by girls rather than boys. Intrusion of words of an extra-list also was lower in girls (mean 1.7%) than in boys (mean 5.1%). In comparison with 7-8 year olds, 13-15 year olds exhibited a higher level of semantic clustering, reflected by their recall of a string of items belonging to the same category before they proceeded to the next category.

Metacognition has also been studied by using the 20 Questions Task of Denny and Denny (1973). This task assesses the capacity to ask higher-level questions that reflect processing of the semantic properties common to a subgroup of animate and inanimate objects, which are presented to the child in a pictorial display. By verbalizing a feature such as a "living thing," older children can ask primarily constraint-seeking questions that eliminate several alternatives (e.g., a fish, dog, tree). In contrast, young children tend to ask hypothesis-type questions (e.g., ”Is it the dog?”), which pertain only to a single item, thus

failing to reflect verbal mediation of features common to two or more of the items. In a cross-sectional study (Levin et al., 1991), the percentage of constraint-type questions asked by normal children increased more than threefold from age 7-8 years to age 13-15 years. Analysis of developmental changes disclosed a corresponding decline in the percentage of hypothesis-type questions in these age ranges. Pseudo-constraint questions (”Is it the one that barks?”), which also eliminated only a single alternative, declined with age in normal children.

Another example of an executive function is planning, which refers to the capacity for setting goals and the ability to maintain an action sequence in working memory (i.e., maintaining a representation of the goal in working memory). The capacity for planning can involve breaking down a complex problem into subsidiary goals, monitoring the attainment of each subsidiary goal, and maintaining the overall solution in working memory. The Tower of London, a test developed by Shallice (1982) is similar to the Tower-of-Hanoi, described in chapter 1.3.1. The complexity of the problems composing this task is determined by the minimum number of moves necessary for a solution. The percentage of problems solved by normal children on the first trial increases with age. While administering the Tower of London, the examiner reminds the child of the rules, such as picking up only one bead at a time. Levin and associates (1994) found that children who had sustained a severe brain injury tended to break the rules despite reminders by the examiner. This tendency to break the rules was particularly notable in the children with TBI who were 6-10 years old at the time of testing. The initial planning time, which is the time from presentation of the problem until the child initiates the first move, may be construed as reflecting impulsivity. However, Levin and coworkers (1994) found that the initial planning time declines with age and is prolonged in children who have sustained a severe brain injury.

Flexibility in problem-solving skills and the ability to profit from environmental feedback are also examples of executive functions. As described in chapter 1.3.1, the WCST (Heaton, 1981) is a classic measure of flexibility in problem solving. Changes in the salient dimension are discovered by the child through attending to the examiner's feedback. Divergent reasoning, which is exemplified by producing exemplars of a category, also involves flexibility in reasoning. Levin and coworkers (1993; 1996) found that children with severe TBI performed less well on these tasks as compared to children with mild to moderate TBI.

1.3.3 Summary

Although children with ADHD and children with TBI both suffer from significant impairments in executive functions, the empirical research examining executive functions in ADHD is much larger compared to the results in brain injured children. It is therefore not surprising that the executive function deficit in ADHD can be more precisely described as a deficit in response inhibition. However, it is still unclear if this deficit in ADHD results from a cognitive or motivational deficit. Due to the behavioral similarities between both groups it seems to be of special interest to determine if children with TBI show a comparable response inhibition deficit. This will be discussed in chapter 3 and 4.

1.4. A RECENT MODEL OF ADH SYMPTOMATOLOGY

Summing up the results from the previous chapters the following etiological model of ADH symptomatology can be proposed. The three core behavioral symptoms, inattention, hyperactivity and impulsivity might be associated with a dysexecutive syndrome (Pennington & Ozonoff, 1996). This executive function deficit consists mainly of a deficit in inhibitory control (Osterlaan et al., 1998) which seems to be related to a functional hypofrontality (Zametkin et al., 1990; Sieg et al., 1995). In turn, the hypofrontality correlates with either structural or biochemical changes in the prefrontal lobes which are, for example, expressed by a reduced frontal blood flow. In terms of brain chemistry, neurotransmitters with a preponderant distribution in the prefrontal regions of the cortex are of special interest. Two main transmitter systems seem to be especially involved in the etiology of ADH symptomatology: the dopamine as well as the norepinephrine systems (Shaywitz et al., 1983; Oades, 1997).

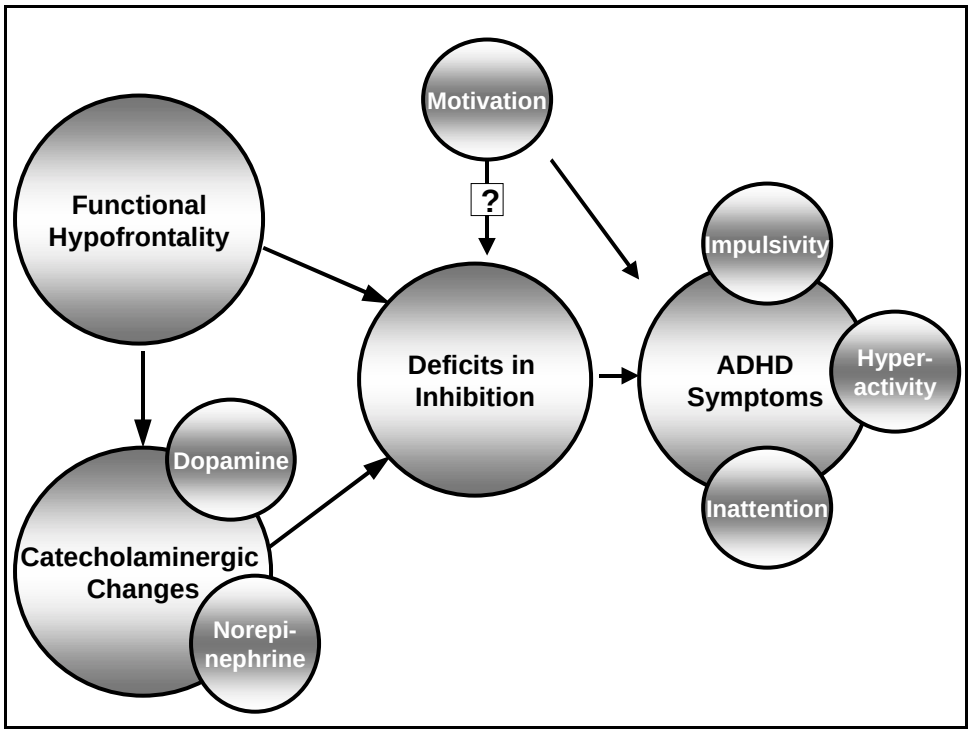

Figure 1.1. Etiological model of ADH symptomatology.

1.5. GENERAL AIMS OF THIS THESIS

The aim of this thesis was to learn more about the underlying cognitive, motivational and neurobiochemical mechanisms of ”disinhibited” symptoms in children with ADHD and children with TBI. Despite the many functional and pharmacological similarities, until now, no research comparing both clinical groups has been carried out.

Based on the model described above, four studies[2] were conducted each of which concentrated on one aspect of this model.

In the introductory chapters, it was described that children with ADHD show considerable overlap with children having suffered from a TBI. Since the response inhibition deficit hypothesis is central in current ADHD research, in the first study it was investigated if this deficit is also present in children with TBI and if TBI children with a deficit in response inhibition also show more ADHD symptoms than those without an inhibitory control deficit (chapter 3).

[2] For better reading, the term “study“ is used although all analyses were carried out on the same sample. However, other terms, such as “experiments” or “exploratory analyses” do not fit for all performed analyses and may therefore be misleading.

In the second study, the hypothesis was tested whether ADHD children's deficits in response inhibition in fact reflect poor motivation compared to TBI children who might show an impairment uninfluenced by motivational factors (chapter 4).

Previous research has suggested that children with ADHD suffer from changes in central catecholaminergic activity. Since both, ADHD as well as TBI children respond positively to stimulant medication the neurobiochemical similarities as well as the differences between ADHD and brain-damaged children were examined in the third study (chapter 5).

The fourth question asks for the relationship between the location of brain lesions and the development of secondary hyper- or hypoactivity in children with TBI (chapter 6).

In chapter 2, the general methods of this thesis are described. If special methods are used in one of the four studies, these will be explained in the corresponding chapter. It should also be noted that all analyses are performed on the same sample. If the sample differs due to missing data or if only a subsample is analyzed as in the 4th study, this will be described in the corresponding chapter.

Chapter 7 summarizes the main findings, discusses the theoretical and clinical implications of this research as well as the limitations of the studies and suggests some avenues for future research.

2. GENERAL METHODS

2.1 SUBJECTS AND SELECTION PROCEDURE

Three groups of subjects with a total of 94 children were examined in the present project. Thirty-one children met DSM-IV criteria for ADHD and had no history of any brain injury, 37 children had suffered from a moderate to severe TBI, 26 were normal controls. Demographic and clinical features of each sub-sample analyzed in the following studies will be presented in the method section of the corresponding chapter.

The ADHD as well as the control subjects were recruited through newspaper advertisements. It is therefore important to keep in mind, that the ADHD group was a community-based sample. All children were aged between 8 and 12 years. Before the children came to our department for assessment, a telephone interview was conducted in order to screen for ADHD symptoms as well as to exclude children with developmental delays, learning disabilities or a subclinical symptomatology of ADHD (more than 4 symptoms of both symptom lists, but below the ADHD threshold). Children with chronic illnesses who were on any type of medication were also excluded.

The sample of head-injured children was recruited from two neurological rehabilitation centers. All participants of this group had experienced a traumatic head injury and received inpatient hospital rehabilitation at the time of testing. This yielded a sample of TBI children with reasonable homogeneity in terms of expected brain pathology. All patients were examined in a chronic stage of recovery, at least 6 months after the head injury. At the time of injury, the children were between 4 and 11 years old. Time between injury and testing ranged from 6 months to 6 years. The head-injured children were screened for pre-existing learning problems and behavior disorders prior to the injury. Exclusion criteria were premorbid mental retardation, premorbid symptoms of ADHD or other developmental disorders.

In the ADHD and control group, the psychopathological status was assessed by two parent interviews and a teacher questionnaire. A German semi-structured diagnostic interview ("Diagnostisches Interview für psychische Störungen im Kindesalter"; K-DIPS, Unnewehr, Schneider & Margraf, 1995) and a German translation of the "Disruptive Module of the Parent Interview for Child Symptoms", PICS, Schachar & Wachsmuth, 1989) were conducted with all parents. The teachers of the participating children were asked to complete a German questionnaire for hyperkinetic disorders (FBB-HKS,

Döpfner, 1998). Children were classified as hyperactive, if they fulfilled ADHD criteria of DSM-IV in the combined rating of their parents and teachers. A symptom was judged as present if it was rated at least with 2 on a four-point-rating scale either by the parents or the teacher.

In the head injured group the premorbid psychopathological status was retrospectively assessed by the parents' ratings in the K-DIPS and PICS. However, since these children were in the hospital for at least three months and had few or no face-to-face-contact with their parents, the current diagnosis of ADHD was considered to be more reliable by the ratings of the staff of the rehabilitation center, especially since this was organized in small family-like living communities. Therefore, the diagnosis of a post-injury ADHD in the head-injured sample was based on the combined rating of the staff and teachers of the rehabilitation center.

2.2 PROCEDURE

All children were tested individually in a quiet room in the presence of an examiner. One parent was simultaneously interviewed by a second examiner. All diagnostic interviews were conducted either by the author or by psychology students with a bachelor degree and a specialization in clinical psychology who had been extensively trained in conducting the diagnostic interviews. All interviews were videotaped and, if diagnostic problems occurred, the author made the decision on the basis of the videotape.

For the ADHD and control children, the assessment was conducted at the Department of Psychology at the University of Marburg. The head-injured children were tested in the rehabilitation center in Bremen. Each child was assessed twice.

At the first appointment, the child's assessment began with the two experimental inhibition tasks. Subsequently, an intelligence test as well as a test of cognitive speed were conducted. To obtain an objective measure of the child's activity the child had a small actigraph at the dominant arm during the whole procedure. Throughout the assessment, the child was videotaped. The child's activity was also measured in two standardized situations.

At the second meeting the two inhibition tasks were repeated either with or without a motivation manipulation (see study 2). In addition, the CPT was administered.

Informed parental consent was obtained for all participants prior to the first assessment.

2.3 BIOCHEMICAL MEASURES

The activity of the norepinephrinergic system was measured by collecting a urine sample before and after conducting the stressful mental tasks on the first day of the assessment.

This peripheral measure of catecholamine activity was examined for several reasons: (1) it is a non-invasive procedure which can be easily applied to children, (2) it can be assessed twice (before and after cognitive stress) and due to its short half-life it reflects the dynamics of norepinephrine (NE) and epinephrine (EPI) activity, (3) a large number of studies has demonstrated the superiority of spontaneous urine samples collected during specific activities compared to studies of catecholamines and their metabolites in 24h-urine, plasma, and cerebrospinal fluid in hyperactive children (Khan & Dekirmenjian, 1981; Mikkelson et al., 1981; Rapoport et al., 1978; Shaywitz, Cohen & Bowers, 1977; Shekim, Dekirmenjian & Capel, 1977; Shekim et al., 1983; Wender et al., 1971).

Urinary catecholamines and metabolites are derived from several sources, both neuronal and non-neuronal, and thus do not represent the activity of a single catecholamine system. Furthermore, only a small fraction of the total amount of each catecholamine produced is excreted unchanged in urine.

The bulk of plasma NE is derived from the sympathetic nerves, with only a few percent coming from adrenal medullary secretion (Esler et al., 1990). Urinary NE is derived primarily from plasma NE filtered at the glomerulus (Kopp, Bradley & Hjemdahl, 1983). An additional contribution is made by tubular secretion of NE released into the interstitium of the kidney by renal sympathetic nerves (Baines & Drangova, 1986).

In contrast to plasma NE, the bulk of plasma EPI is derived from the adrenal medulla (Cryer, 1980; Shah et al., 1984). EPI is excreted in urine approximately in proportion to its glomerular filtration from plasma although possibly subject to modification by tubular secretion (Baines & Drangova, 1986). Thus, differences in urinary catecholamine excretion may be due to numerous biochemical and physiological processes, some of which are unrelated to sympathoadrenal medullary secretion.

However, the argument that urinary catecholamine measures are derived from peripheral sympathetic nervous system and therefore are not of any value in mental disorders has to be considered with caution.

The noradrenergic system consists of two components: (1) the central NE system which originates primarily in the locus coeruleus (LC) and (2) the peripheral sympathetic NE system, which originates in the intermediolateral cell column of the spinal cord. NE projections from the LC innervate the entire cerebral cortex and midbrain as well as the spinal cord. LC projections do, however, not make direct contact with the intermediolateral cell areas (Holets, 1990). These LC sympathetic systems are independent, yet they interact in ways that are yet not entirely understood. Some of the noradrenergic fibres of the brain stem project into these areas, here central NE has an impact on the peripheral nervous system (Loewy, 1990).

Peripheral catecholamines can be studied not as a direct but as an indirect indicator of the activity of the central nervous system. This is due to the fact that the locus coeruleus and the intermediolateral cell areas receive similar inputs. Maas and Leckman (1983) showed in their review that an activation of the LC induced an increased excretion of peripheral NE of the sympathetic nervous system. Vice versa, a manipulation of the sympathetic nervous system has central effects. For instance, a peripheral EPI-injection is followed by an improvement of learning performance in animal studies (e.g., Sternberg, 1985) as well as in human beings (e.g., Van Zijderveld et al., 1993), although the peripheral EPI cannot pass the blood-brain-barrier.

Thus, although the peripheral and the central catecholaminergic systems do interact, this interaction is not large enough for urinary catecholamines to reflect central LC-activity. However, they do have effects on behavior and performance.

This is, however, not the case for dopamine activity. The urinary excretion of dopamine (DA) greatly exceeds that attributable to filtration from plasma at the glomerulus. The surfeit largely derives from the conversion of DOPA to DA by decarboxylation in the proximal renal tubules (Baines & Drangova, 1985). Therefore, a large fraction of the urinary DA metabolite pool is derived from two sources unrelated to the function of DA as a neurotransmitter. The first source is from DA in sympathetic nerves where it is a precursor of NE synthesis and not a neurotransmitter. The second source is from DA synthesized in the proximal renal tubules (Kopin, 1985). Therefore, there is not enough evidence that central dopaminergic activity can be assessed by peripheral measures, such as blood plasma or urine samples.

In the present project, the spontaneous eye blink rate was thus used as an indirect indicator of central dopaminergic activity. The relationship between eye-blink rate and central dopamine activity has been demonstrated by a series of studies (for review see

Karson, 1983). First, apomorphine and other dopamine agonists acutely increase blink rate in monkeys, an effect blocked by sulpiride (a D_2 blocker). Second, Parkinson patients with levodopa-induced dyskinesia exhibit twice the mean blink rate of other Parkinson patients whereas the more symptomatic of the nondyskinetic patients have a very slow rate. Third, schizophrenic patients have an elevated mean blink rate normalized by neuroleptic treatment.

2.4 ASSESSMENT OF COGNITIVE FUNCTIONS

2.4.1 General intelligence

Raven's Progressive Matrices (Raven, 1976; 1979) were used as an IQ test. The Colored Progressive Matrices (CPM) were administered to children under the age of 11, children older than 11 were assessed with the Standard Progressive Matrices (SPM).

Raven's Progressive Matrices are a popular measure of conceptual ability because responses require neither verbalization, skilled manipulative ability nor subtle differentiation of visuospatial information. In addition, verbal instruction is kept to a minimum.

The SPM consist of 60 items grouped into five sets (A to E), each set containing 12 items. Each item contains a pattern problem with one part removed and 6 to 8 pictures inserts, one of which contains the correct pattern. Each set involves different principles of matrix transformation, and within each set the items become increasingly more difficult.

The CPM provide a shorter and simpler form of the test. The test consist of 36 items, grouped into three sets (A, Ab, B) of 12 items each. It was developed for use with younger children (age 5,5+). The problems are printed on colored backgrounds in order to attract the subject's attention.

Both tests were applied individually without time limit in the paper and pencil form. Scores were converted into percentiles according to age- and school-based norms.

Test-retest reliability data for both test versions are acceptable (above 0.8). The medium test-retest values are between .64 and .93 with the lower values for retest intervals over one year. The Raven Tests show a moderately high correlation with other IQ measures, such as the WISC-R (range between .48 and .73).

The majority of the brain-injured children also received the Wechsler Intelligence Scale for Children - Third Edition (ages 6-16), which has been standardized on large samples and displays excellent reliability and validity (Wechsler, 2983).

2.4.2. Cognitive speed: Zahlen-Verbindungs-Test (ZVT)

The ZVT (Oswald & Roth, 1978) is a short test for examining a person's cognitive speed. It is comparable to version A of the Trail Making Test (TMT, Lezak, 1995). Subjects are asked to connect as fast and as accurately as possible a series of 90 numbered circles distributed arbitrarily over a page. The test consists of four matrices, and the mean speed for each matrix is calculated as the score.

Normative data are available for children and adults, aged 8 to 60 and scores can be converted into T-scores, stanines or percentage norms.

The test was administered individually. Retest-reliability for the individual administration is about .95, the internal consistency ranges from .95 to .97. Correlations with IQ measures vary between .43 and .83

2.5 PSYCHOPATHOLOGICAL ASSESSMENT

2.5.1 Diagnostisches Interview bei psychischen Störungen im Kindes- und Jugendalter (K-DIPS)

The "Diagnostische Interview bei psychischen Störungen im Kindes- und Jugendalter (Kinder-DIPS)" was published by Unnewehr et al. (1995). It is a semi-structured interview for diagnosing the most common mental disorders in children aged between 6 and 18 years according to DSM-IV, for instance externalizing behavioral disorders, anxiety disorders, affective disorders. Two screening instruments for specific learning disabilities and psychosis are included. The K-DIPS provides two versions for assessing the child's self-report and the parents' rating or rating of another educating person. The duration is about 60 minutes. The interrater reliability for categorial diagnosis was found to be 89 to 100% for the parents' version and 84 to 100% for the children's version. A comparison of reliabilities specific to disorders showed that for externalizing behavior disorders the parent version showed higher reliabilities, whereas reliabilities were comparable for the other disorders. A validation of the K-DIPS was performed using the German version of the Child Behavior Checklist (CBCL, Remschmidt & Walter, 1990) and a high correlation between DIPS-diagnosis and concordant symptoms in the CBCL was reported.

In the present project, only the parents‘ version of the K-DIPS was used due to its better reliability with respect to externalizing behavior.

2.5.2 Parent Interview for Child Symptoms (PICS)

The unpublished Parent Interview for Child Symptoms (PICS) was developed by Schachar and Wachsmuth (1989). It is a semi-structured diagnostic instrument for the diagnosis of disruptive behavior disorders (ADHD, ODD, and CD) and screens for diagnoses of other emotional and psychiatric disorders. The interview is designed to permit the development of rapport with the informant and a precise understanding of the nature of each child's mental disorder. Rather than coding the exact response of the informant as is typically done in current structured diagnostic interviews, the PICS aims to probe the informant's response in sufficient detail to be able to separate child behavior from informant bias, impression or perceptions. The terms and the description of syndromes and symptoms follows that of DSM-IV. The PICS consists of a General Information Module, a Disruptive Behavior Module, and a General Psychopathology Module.

Schachar et al. (1995) found an interrater concordance for the diagnosis ADHD, ODD and CD of 100% within 35 diagnostic interviews. Differences were only found in respect to symptom severity. High correlations were found between ADHD symptoms in the PICS and a parent rating scale ($r = .65$, $p < .001$). This was also true for ODD ($r = .68$, $p < .001$) and for CD ($r = .44$, $p < .001$).

In the present project, only the Disruptive Behavior Module was used since general psychopathological status was already assessed with the K-DIPS. To enhance concordance, it was translated into German by the author and retranslated by a native speaker. The author took part in an extensive interview training and trained the other examiners until interrater reliability was above 0.8.

2.5.3 Fremdbeurteilungsbogen für hyperkinetische Störungen (FBB-HKS)

The “Fremdbeurteilungsbogen für hyperkinetische Störungen (FBB-HKS)” is a German behavioral rating for ADHD symptomatology, according to DSM-IV and ICD-10 and was developed by Döpfner and Lehmkuhl (1998). The rating can be performed by teachers, educators or parents. The scale consists of 20 items, for each item the severity has to be rated on a four-point rating scale. For each symptom a rating of how problematic the

behavior appears to be is added. The internal consistency in a clinical study was found to be .88 for the severity-scale and .89 for the problem scale.

2.6 ACTIVITY MEASUREMENT

To date, the most accurate measures of hyperactivity are provided by portable electronic activity monitors (actigraphs). Previous studies have found that children with ADHD are about 25 to 30% more active than normal controls, particularly during performance of laboratory-based attentional tasks (Halperin et al., 1994) or during academic classroom activities (Pororrino et al., 1983). Therefore, during the whole assessment of the first day, the children were asked to wear a tiny actigraph, the size of a watch on their dominant arm (Cambridge Neurotechnology, Version 2.56). The actiwatch measured the activity with an epoch length of 0.25 minutes. A total score of activity per hour was calculated.

2.7 EXPERIMENTAL PROCEDURES

2.7.1 Stop Signal Task

A laboratory analog of a situation requiring inhibitory control in the sense of stopping an ongoing action is the Stop Signal Paradigm. The task is assumed to directly measure the mechanisms of inhibition (Logan, 1994). Subjects engaged in a reaction time task demanding fast and accurate responses (primary task) are occasionally presented with an auditory stop signal, telling them to inhibit their response to the primary task stimulus. The stop signal occurs at varying delays after the onset of the primary stimulus. The shorter the delay, the easier it becomes to inhibit the response; the longer the delay, the more difficult it becomes to inhibit the response. The primary task stimulus can be regarded as the impetus for the impulse, and thus the response to the primary task can be interpreted as the prepotent response. The stop signal is a control signal that renders the prepotent response inappropriate. From this point of view, “inhibiting when given a stop signal is evidence of good impulse control, and failing to inhibit when given a stop signal is evidence of poor impulse control” (Logan, Schachar, & Tannock, 1997, p. 60). In the Stop Task, the 'go' and 'stop' stimuli are clearly distinguishable, whereas in real world situations the requirements of stimuli that elicit impulsive behavior and those that inhibit it might not be as easily to detect. Another advantage of the Stop Signal Paradigm is that it allows for a

clear definition of the changes that result from executing the response successfully (i.e., absence of overt behavior, inhibition of the response) and that it provides a way to measure the latency of the act of control (i.e., the stop signal reaction time, SSRT).

The Stop Task is based on a well-established theory of inhibition, known as the horse-race model (for a review, see Logan, 1994; Logan, Cowan, & Davis, 1984). Its basic assumption is that response inhibition is a probabilistic process, depending on a race between the processes responding to the go stimulus and the processes responding to the stop stimulus. Depending on which process finishes first, the response is either executed or inhibited.

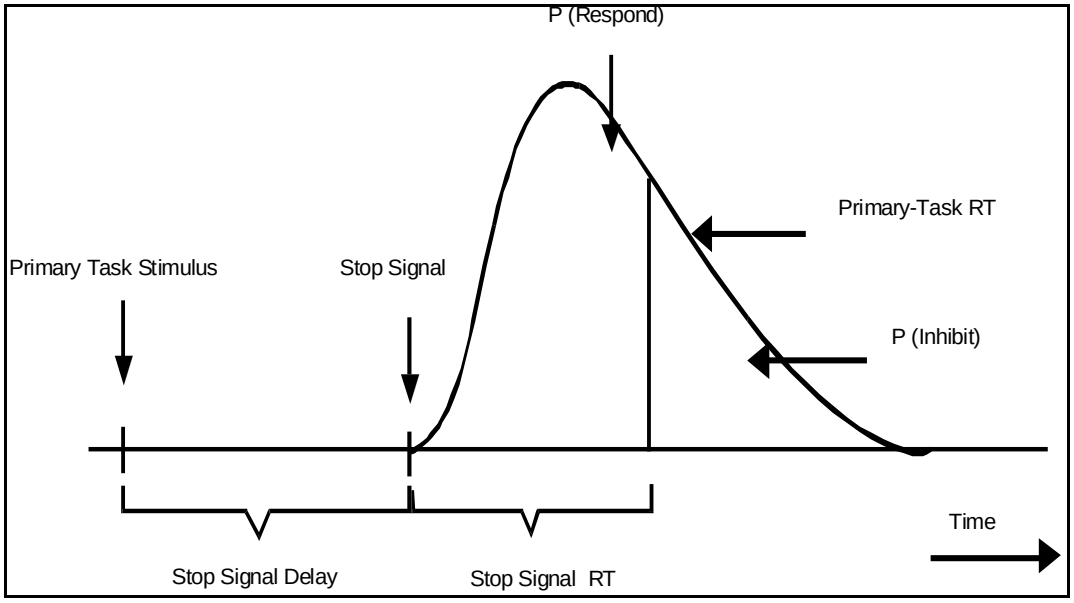

FIGURE 6.1. HORSE-RACE MODEL ACCORDING TO LOGAN AND COWAN (1984).

As illustrated in Figure 6.1, several factors determine the outcome of the race: (a) the delay between the onset of the stimulus for the primary task and the onset of the stop signal (stop-signal delay), (b) the mean RT to the primary task, (c) the mean RT to the stop-signal, and (d) the variance of RT to the primary task (Logan, Cowan, & Davis, 1984, p. 277). Thus, according to the model, poor inhibitory control could result from responding too quickly to the go signal or responding too slowly to the stop signal.

2.7.2 Tracking procedure

Unlike go-signal reaction time, stop-signal reaction time cannot be measured directly. Subjects either inhibit or fail to inhibit when a stop signal is presented. If they fail

to inhibit, stop-signal reaction time must have been slower than the observable latency of the go-signal response, but it is not clear how much slower it was if they succeed in inhibiting. Stop-signal reaction time must have been faster than go signal reaction time, but neither the stop process nor the go process provides an observable response with a measurable latency. Something beyond direct observation is required.

The race model of the Stop Signal Paradigm provides at least three different ways to estimate stop-signal reaction time (see Logan, 1994). Here, a fourth method for estimating stop-signal reaction time was used, also derived from the race model. This tracking procedure is easier to compute and to understand than the other methods (first described by Osman, 1986 and Logan et al., 1997).

In stop-signal experiments, researchers vary the delay between the stop signal and the go signal (stop-signal delay) in order to favor one process or the other. Most often, stop-signal delays are selected at random from a fixed set that is held constant throughout the experiment (e.g., Logan & Cowan, 1984), but many researchers let them vary dynamically, contingent on the subject's behavior (e.g., Osman et al., 1986; 1990; Schachar & Logan, 1990; Schachar et al., 1995). The new method for estimating stop-signal reaction time uses a tracking procedure in which stop-signal delay changes after every stop-signal trial, increasing by 50 ms if subjects succeed to inhibit and decreasing by 50 ms if they respond. This tracking procedure, introduced by Osman et al. (1986; 1990), converges on a stop-signal delay at which signals inhibit 50% of the time. That delay is important because it represents the amount of handicapping necessary to “tie” the race. At that delay, the stop process and the go process finish at the same time, on average, and which one wins on a particular trial depends on random variation. Thus, that delay is the average point in time at which the stop process finishes, and that information can be used to estimate stop-signal reaction time.

The estimation of stop-signal reaction time is illustrated in Figure 6.2. The race depends on three quantities - go reaction time, stop-signal reaction time, and stop-signal delay - and the experimenter knows two of them. Moreover, because subjects inhibit 50% of the time at the critical delay, stop-signal reaction time plus stop-signal delay must be equal the mean go reaction time. Stop-signal reaction time can thus be calculated simply by subtracting the stop-signal delay from the mean go reaction time.

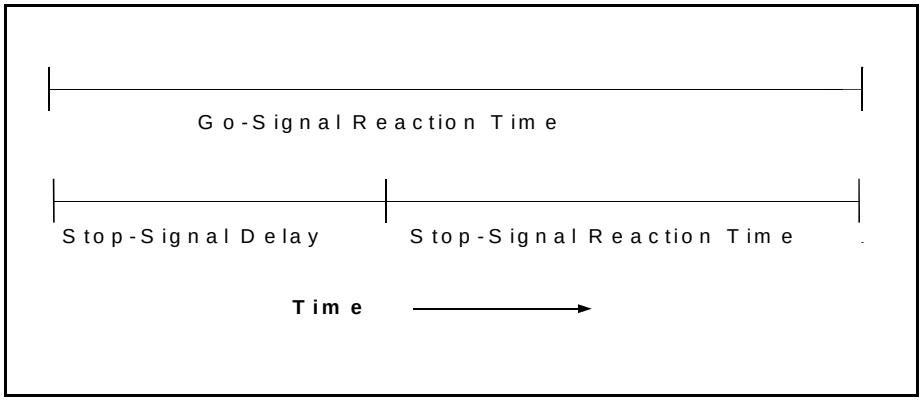

FIGURE 6.2. ESTIMATION OF STOP-SIGNAL-REACTION TIME ACCORDING TO THE TRACKING PROCEDURE.

2.7.3 Child-appropriate modification of the Stop Signal Task

In the present studies, the go- task in the Stop Signal Task was a two-choice reaction task in which an Unknown Flying Object (UFO) appeared to the left or right of a fixation cross. The children had to respond with the appropriate mouse button on a two-button response-box depending on the side where the UFO was presented. They were told to inhibit their response whenever the stop-signal, a 1kHz tone of 500 ms duration presented through earphones, appeared. Children were instructed to respond as fast and accurately as possible to the UFOs and not to wait for the stop-signal. The modification of the task is illustrated in Figure 6.3.

The procedure started with two practice blocks, thereafter trials were presented in eight blocks, each consisting of 40 trials. Twenty-five percent of the trials were stop-trials, 75% were go trials. The intertrial interval was set at 1000 ms. Left and right sided presentation occurred randomly with equal frequency in all conditions. After each block a blank screen appeared allowing the children to rest. The mean go reaction time of the previous block was displayed on the screen after each block giving the participants feedback about their performance. If they slowed down they were again instructed not to wait for the stop-signal. The response window was 1000 ms. If there was no response within this interval the feedback “too late“ appeared on the screen and trials were repeated at the end of the block.

The stop-signal delay was set at 300 milliseconds initially and then adjusted dynamically in 50 ms increments depending on the child’s behavior: increase for successful inhibition, shortening for failure.

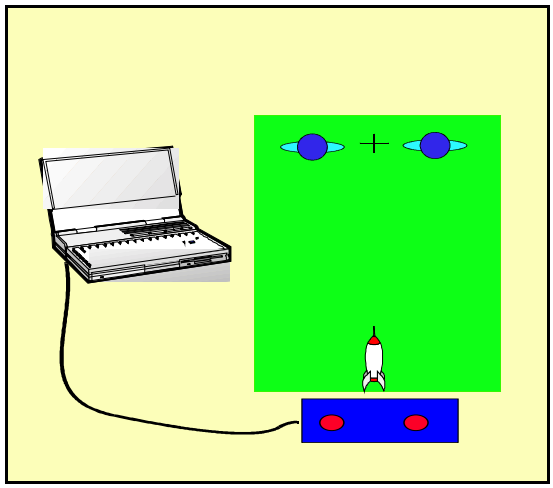

Figure 6.3. Modification of Stop Task.

2.7.4 Delay Task

In order to measure response inhibition of prepotent but not already initiated reactions a Delayed-Response Task was developed. The conflict between the valences of an immediate versus later outcome was established by an instruction to wait and contrasted with the possibility of the child reacting impulsively to the stimulus without waiting. The computer screen was divided into an upper red and a lower green area (corresponding to stop and go as in traffic lights). UFOs flew down diagonally from a central point in the red area to the left or right side of the screen. Children were asked to press the appropriate button of the response box depending on the UFO's flight direction, as soon as the UFO reached the green area. The red area was called the "forbidden area", where children were not allowed to fire on the UFO. There was a high and a low speed for the UFOs, with a correspondingly longer wait for the slower speed. The two speeds were altered randomly, but occurred with the same frequency. If children pressed the button too early (while the UFO was still in the red area), the screen darkened for 500 ms before a new UFO appeared. The Delay Task is illustrated in Figure 6.4.

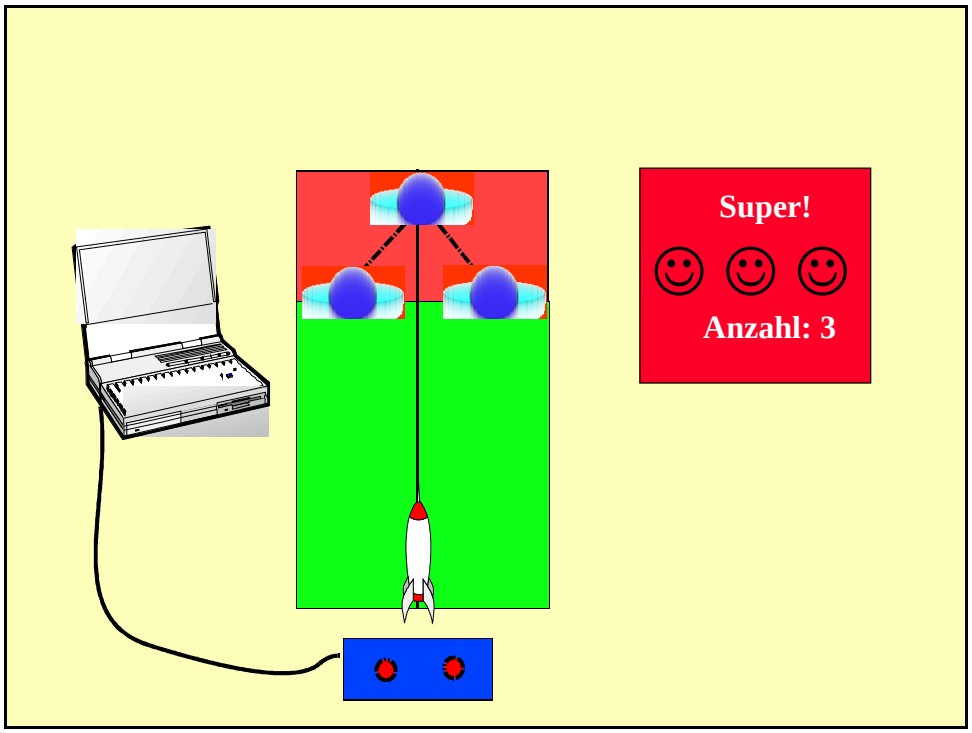

Figure 6.4. Delayed-Response Task.

The task consisted of 80 trials, presented in two blocks, after one practice block with 16 trials was conducted. The reaction time window (after the UFO had reached the green area) was 800 ms. Dependent variables were the percentage of successful inhibition (not firing before the green area was reached) as well as the reaction times calculated separately for the two delays.

2.8 GENERAL CONSIDERATIONS FOR DATA ANALYSIS

The data analysis was performed using SPSS for windows. Classification and regression trees (CART) were conducted with the Answer Tree Program of SPSS (a detailed description of this method will follow in chapter 6.4).

In general, three groups of children (ADHD, TBI, controls) were compared. Further subgroup analysis were conducted in chapter 3 and 5. Group comparisons were performed by multivariate analyses of variance (MANOVAs) or analyses of variance (ANOVAs), depending on the degree of correlation among the dependent variables. If dependent variables are uncorrelated, a multivariate approach may lack power (Keppel, 1991).

First, it was tested whether the variables were normally distributed and did not violate further assumptions of statistical tests, such as multivariate normality, homogeneity of variance-covariance matrices, linearity, homogeneity of regression, multicollinearity and singularity in MANOVA procedures.

In chapter 4 and 5, univariate and multivariate repeated measure analysis of variance were conducted to analyze the effects of a within-task experimental manipulation between the groups.

Since the present research in the field of TBI does not allow to formulate directed hypotheses, significant group effects were usually followed up with Tukey's studentized range (HSD) instead of group contrasts. This procedure tests for significant differences between groups and controls type I experimentwise error rate.

When effect sizes were calculated, as in chapter 4, omega squared (ω^2) was used to estimate treatment magnitude, since this measure includes the strength of association between the independent (IV) and dependent (DV) variable in the population in contrast to other effect sizes (e.g., η^2), and not only in the sample (Tabachnick & Fidell, 1996). However, there are some problems in estimating ω^2 in repeated measures- designs with respect to the definition of the relevant variance components. Following the recommendations of Keppel (1991), ω^2 was calculated according to the concept of partial omega squared:

$$\omega_A^2 = \frac{\sigma_A^2}{\sigma_A^2 + \sigma_{error}^2}$$

with:

$$\sigma_A^2 = \frac{df_A\left(MS_A - MS_{A\times S}\right)}{(a)(n)}$$

and:

$$\sigma_{error}^2 = MS_{A\times S}$$

3. INHIBITORY CONTROL IN CHILDREN WITH ADHD AND CHILDREN WITH TBI

3.1 INTRODUCTION

In contrast to the extensive research on response inhibition in ADHD (see also chapter 1.3.1), few empirical studies have examined inhibitory control in brain injured children. Dennis, Wilkinson and Koski (1995) showed that children with closed head injuries had a reduced ability to inhibit prepotent response tendencies using the Delay Task of the Gordon Diagnostic System (GDS). In addition, brain injured children were shown to suffer from a deficit in understanding deceptive emotions in narratives, an ability which depends on discourse comprehension, metacognition as well as cognitive inhibition (Dennis, Barnes & Wilkinson, 1998). In a recent study of attentional deficits in children with TBI, Anderson, Fenwick and Manly (1998) examined different aspects of attention, namely: sustained, focussed and divided attention, and response inhibition. Results indicated that attentional skills may be differentially impaired after TBI, with children who have sustained moderate-to-severe TBI exhibiting significant deficits in sustained and divided attention, and response inhibition, but having relatively intact focussed attention.

As described in chapter 1.3, Barkley (1997) distinguishes three forms of response inhibition: (1) inhibiting prepotent responses, (2) stopping an on-going-response, and (3) interference control and argues that ADHD involves a pervasive deficit in all forms of response inhibition. A reliable and valid method of measuring pure inhibition is the Stop-Signal Task (Logan & Cowan, 1984; Logan, Cowan & Davis,1984). Since the stop signal always appears after the primary stimuli has been presented, this task is purported to assess the ability to interrupt an ongoing response and therefore represents an operationalization of an “ongoing-response“- inhibition task, according to Barkley’s model (Barkley, 1997). A second aspect of inhibition in Barkley’s model refers to the inhibition of prepotent but not already initiated responses. It can be best examined in tasks such as delayed response tasks, which represent a conflict between immediately rewarding outcomes that lead to later and larger punitive ones or immediately aversive ones that lead to later and larger rewarding outcomes (Barkley, 1997).

There is only one study comparing adults with Attention Deficit Disorder (ADD) to adults with mild closed head injuries (mCHI) using neurobehavioral performance tasks (Arcia & Gualtieri, 1994). The authors showed that although both clinical groups had

significantly more difficulties with sustained attention than controls, the mCHI group was characterized by a generalized slowness in their responses, whereas the ADD group mainly suffered from impulsivity or an inability to regulate their attention and responses.

Therefore, the aim of this study was to compare the functioning of two types of response inhibition[3] in children with ADHD to children with TBI as well as to a group of matched controls. With respect to Barkley's model deficits of inhibitory control were assumed to be present in both types of inhibition.

Since it has been shown that children with TBI have a four to five times greater risk of developing a postinjury ADHD (Brown, Chadwick & Shaffer, 1991; Max, Robin & Lindgren, 1997) subgroup analyses with TBI children who have developed a secondary ADHD and children who do not fulfill the ADHD criteria are necessary. Given the results of the study by Arcia and Gualtieri (1994) it was assumed that in the stop-signal-task children with TBI would probably be generally slowed in their stop- and their go-processes, whereas the ADHD children would only suffer from a specific deficit in their inhibitory control process. However, TBI children who have developed a secondary ADHD were expected to show a dissociation between stop- and go-processes comparable to ADHD children without a history of brain damage. For the Delay-Task, a "delay-dose"-relationship was assumed, with poorer performance resulting from longer delays in children with ADHD and children with TBI. Again, TBI children were also expected to have longer MRTs in the Delay-Task.

3.2 METHODS

3.2.1 Data analyzed in the present study

A total of 84 children participated in this experimental study. Thirty-one children met DSM-IV criteria for ADHD and had no history of brain injury, 27 children had suffered from a moderate to severe TBI, 26 were normal controls. 13 (48%) of the TBI children had developed a secondary ADHD after the accident. The demographic and clinical features of the three groups are described in Table 3.1. Groups were comparable with respect age ($F(2, 81) = 1.1$, $p = .3$), to sex (χ^2, $=3.6$, $p = .16$) and general IQ ($F(2, 81) = 1.7$, $p = .2$). As expected from prior research, groups differed in the cognitive speed of the NCT ($F(2, 81) = 8.4$, $p < .01$). Post-hoc analyses showed that TBI and ADHD

[3] For the purpose of this experiment, only prepotent and on-going response inhibition was examined, ignoring the third aspect (interference control) of Barkley's model.

children had a significantly lower T-value in the NCT compared to normal controls (ADHD < controls: $p < .05$, TBI < controls: $p < .01$).

Table 3.1.
Demographic and clinical features of children with TBI, ADHD and control children.

	Groups		
	TBI (n=27)	ADHD (n= 31)	Controls (n=26)
	M (SD)	M (SD)	M (SD)
Number of males	19	28	20
Age at testing (years)	10.6 (1.7)	10.5 (1.6)	10.2 (1.2)
Raven-IQ	94 (14)	95 (13)	102 (13)
Number Connecting Test (T-Value)	45 (12)	48 (8)	54 (12)
Total score of activity (per hour) [a]	3625 (2519)	5203 (2293)	3611 (1772)
Number of			
Inattentive symptoms (total: 9)	4.7 (2.8)	6.7 (2.3)	0.5 (1.0)
Hyperactive symptoms (total: 6)	1.8 (2.1)	4.0 (2.1)	0.6 (1.4)
Impulsive symptoms (total: 3)	1.2 (1.2)	1.9 (1.3)	0.1 (0.2)
Subjects fulfilling DSM-IV criteria for			
ADHD inattentive subtype	7	9	0
ADHD hyperactive-impulsive subtype	0	4	0
ADHD combined subtype	6	18	0

[a] Arbitrary units.

3.2.2 Statistical analyses

Before conducting statistical analyses, variables were explored for assumption violations. Examination of task performance by group revealed that some variables were skewed or were from non-normal populations for two if not all three groups. A decision was made to recode outliers to two standard deviations above or below variable means, and when required further transformations (log or 1/sqrt) were performed, as it is recommended by Tabachnick and Fidell (1996). This process reduced satisfactorily the skewness of measures. Multivariate analyses of variance (MANOVA) were then conducted separately for the two experimental paradigms. Critical alpha for the Wilk's lambda statistics was adjusted to .025 to account for the fact that two inhibition paradigms were used. Significant group effects were followed up with Tukey's studentized range (HSD). Further univariate analyses of variance (ANOVA) and t-tests for independent groups were conducted for the TBI subgroups depending on the number of subgroups. A decision against multivariate analysis of variance for analyzing TBI subgroups was made since the

dependent variables for both inhibition tasks were detected as uncorrelated. Therefore, a multivariate test may lack power (Tabachnick, 1996). To control of familywise type I error, Bonferroni corrections to each test in a set of separate ANOVAs on each dependent variable were applied.

3.3 RESULTS

Descriptive statistics for inhibitory task performance for ADHD, TBI and controls as well as data separated for TBI children with (n = 13) and without a secondary ADHD (n = 14) are presented in Table 3.2. As can be seen, the TBI group had the longest reaction times in both tasks, followed by the ADHD and control children. TBI children who had developed a secondary ADHD performed similar to TBI children who did not fulfill criteria for ADHD.

Table 3.2.
Descriptive statistics for inhibitory task performance of ADHD, TBI, and control children.

	Stop-Signal Task		Delay Task			
			Speed 1		Speed 2	
	SSRT [ms]	MRT [ms]	% Inh.	MRT [ms]	% Inh.	MRT [ms]
	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD) [a]
Groups						
TBI	455 (113)	705 (77)	88 (7)	460 (109)	87 (7)	303 (85)
ADHD	431 (77)	612 (59)	89 (8)	391 (66)	85 (8)	231 (50)
Controls	357 (76)	572 (69)	92 (6)	381 (79)	85 (11)	204 (51)
TBI + ADHD	435 (69)	675 (67)	89 (7)	438 (101)	88 (6)	295 (80)
TBI – ADHD	473 (143)	734 (78)	87 (7)	482 (116)	87 (9)	311 (92)

SSRT = stop signal reaction time; MRT = mean go reaction time; % Inh. = percentage of successful inhibition.
[a] original Mean (SD) is presented here (i.e., before outliers were recoded for analysis).

3.3.1 Inhibitory performance in ADHD, TBI and control children

Table 3.3 shows the results of the two multivariate MANOVAs and the post hoc tests for each experimental paradigm and all groups.

Table 3.3.
F-values and significance levels for all comparisons of task performance.

	Wilks Lambda		Main effect		Tukey's HSD
	F	d.f.	d.f.	F	significant differences
Stop task	*15.8*	*4, 160* [a]			
SSRT			2, 81	11.30 [a]	TBI > control [a], ADHD > control [a]
MRT			2, 81	26.40 [a]	TBI > control [a], TBI > ADHD [a]
Delay-Task	*7.1*	*8, 156* [a]			
Speed 1/ long delay					
% Inhibition			2, 81	12.80 [a]	ADHD < control [a], TBI < control [a]
MRT			2, 81	6.68 [b]	TBI > control [c], TBI > ADHD [c]
Speed 2/ short delay					
% Inhibition			2, 81	0.85	
MRT			2, 81	17.75 [a]	TBI > control [a], TBI > ADHD [a]

SSRT = stop signal reaction time; MRT = mean reaction time.
[a] $p < .001$, [b] $p < .002$, [c] $p < .025$.

There were significant group effects in both inhibition tasks: stop task ($F(4, 160) = 15.3$, $p < .001$) and delay-task task ($F(8, 156) = 6.07$, $p < .001$). In the stop-task, the ANOVA revealed significant group effects for the Mean Reaction Time (MRT) ($F(2, 81) = 26.6$, $p < .001$) and the Stop Signal Reaction Time (SSRT) ($F(2, 81) = 11.65$, $p < .001$). The following Tukey's studentized range (HSD) tests showed that for MRT, there was no significant difference between the control and ADHD group, but both these groups differed significantly to the TBI group. Concerning SSRT, there was no significant difference between the TBI and ADHD groups, but both groups differed significantly to the control group.

In the Delay task, the ANOVA revealed significant group effects for percentage of inhibition only in the long-delay-condition ($F(2, 81) = 8.6$, $p < .001$). The following Tukey's studentized range (HSD) tests showed that both clinical groups inhibited less in the "slow-speed-condition" (Speed 1) than the controls (TBI< controls, $p = .002$; ADHD < controls, $p = .001$). With regard to percentage of inhibition, no significant group differences were observed in the short-delay-condition. ANOVA procedures for MRTs in the Delay Task revealed significant group effects for both delay-conditions (MRT speed 1:

F (2, 81)= 6.68, p = .002; MRT speed 2: F (2, 81)=17.75, p < .001). Post-hoc tests indicated that the TBI group had significantly longer MRTs than ADHD (p < .001) and control children (p< .001), whereas there was no significant group difference between ADHD and control children.

To control if the data of the Delay Task were biased by a speed-accuracy trade-off, the correlation between percentage of inhibition errors and MRTs were calculated separately for the two delay-conditions. No speed-accuracy-trade-off was found over all three groups, neither for the long delay- (r = .003, p = .97) nor for the short-delay-condition (r = -.09, p = .38).

In order to determine whether the TBI group suffered from a general slowing in the stop-, as well as in the go-process, the scatterplot of MRT and SSRT for the TBI group is presented in Figure 3.1. The slowing can occur in either process independently of the other.

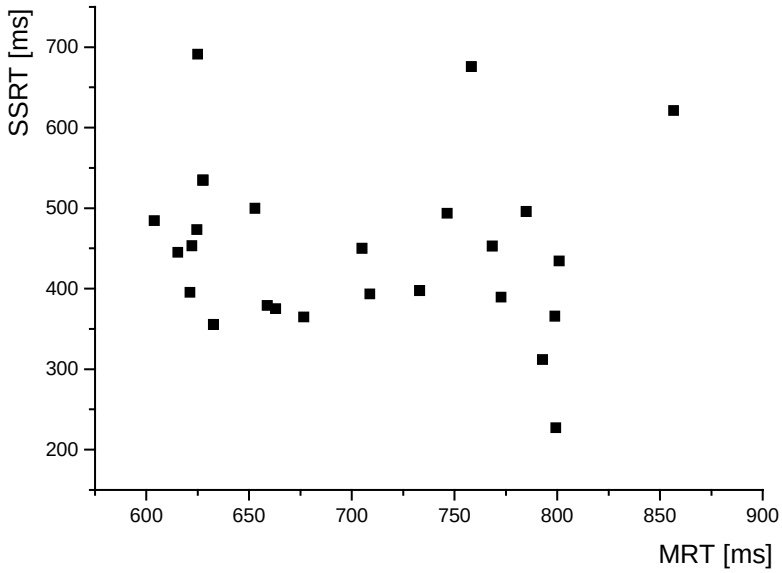

Figure 3.1. Scattergraph of stop- and go-processes in children with TBI. SSRT = stop signal reaction time; MRT = mean go reaction time.

3.3.2 Subgroup analyses I: Inhibitory performance in TBI children with and without secondary ADHD

T-tests for independent groups were performed to compare the two TBI subgroups. Contrary to the expectations, t-tests for independent groups revealed no significant group differences for SSRT between TBI children with and without a postinjury

ADHD (SSRT: t = .57, df = 25, p = .56). However, there was a tendency for the MRT in the stop task to be longer in TBI children without a secondary ADHD (t = 2.1, df = 25, p = .05). No significant group differences for any dependent variable in the Delay task were observed (long delay: % inhibition: t = .58, df = 25, p = .57; MRT: t = .96, df = 25, p = .35; short delay: % inhibition: t = .05, df = 25 , p = .96; MRT: t = .96, df = 25, p = .35).

3.3.3 Subgroup analyses II: Inhibitory performance in hypoactive, hyperactive and normokinetic TBI children

The activity data showed a larger variance in the TBI group than in the other groups with a number of children who showed a total activity score which was at least 1.5 SDs below the average of the controls suggesting that not only hyperactivity but also hypoactivity should be taken into account. Therefore, the TBI group was divided into three subgroups according to their activity level. More than 1.5 SDs below the average they were classified as hypoactive (n=9), more than 1.5 SDs above the average as hyperactive (n=8), the rest was called normokinetic (n=10).

Descriptive statistics as well as statistical results for the inhibition tasks are presented in Table 3.4.

Table 3.4
Mean, standard deviations, and F values for inhibitory task performance in TBI subgroups based on activity levels.

	Hypoactive (n=9)	Normokinetics (n=10)	Hyperactive (n=8)	F value[e]	Post-hoc
	Mean (SD)	Mean (SD)	Mean (SD) [a]		
Activity Score					
Total Score/ hour	782 (98)	3566 (592)	6900 (676)	295.7 [b]	hypoactive < normokinetic < hyperactive
Stop-Signal Task					
SSRT	513 (153)	385 (71)	477 (47)	3.9 [d]	hypoactive > normokinetic
Primary RT	760 (62)	695 (77)	653 (56)	5.8 [c]	hypoactive > hyperactive
Delay Task					
Speed 1					
% Inhibition	83.4 (6.1)	92.2 (4.5)	83.7 (7.5)	7.6 [c]	hypoactive < normokinetic, hyperactive < normokinetic
Primary RT	544 (81)	399 (90)	434 (71)	7.4 [c]	hypoactive > normokinetic hypoactive > hyperactive
Speed 2					
% Inhibition	85.4 (9.8)	89.1 (4.9)	88.9 (6.5)	.4	
Primary RT	326 (88)	276 (85)	310 (74)	1.1	

SSRT = stop signal reaction time; Primary RT = mean reaction time.
[a] original Mean (SD) is presented here (i.e. before outliers were recoded for analysis). [b] $p < .001$, [c] $p < .01$, [d] $p < .025$, [e] d.f. = (2; 24).

In the Stop Task, the hypoactive children showed the longest MRTs and SSRTs, indicating that both, their go- as well as their stop- processes seemed to be slowed down. Hypoactive children had significantly longer MRTs compared to hyperactive children ($p = .029$). In addition, hypoactive TBI children were significantly slower in their stop-process compared to normokinetic TBI children ($p = .007$). The hyperactive children showed the strongest dissociation between a normal (unremarkable) MRT and a long SSRT. The relationship between stop- and go-processes was controlled by calculating the correlation between MRT and SSRT separately for the three subdivisions, but no significant correlations were found.

In the Delay Task, differences were found in the long-delay-condition with hyperactive ($p = .018$) and hypoactive children ($p = .011$) giving poorer inhibitory performances than normokinetic TBI children. In addition, hypoactive TBI children showed significantly longer MRTs in the long-delay-condition than the normokinetic ($p = .003$) and the hyperactive TBI children ($p = .048$).

3.4 DISCUSSION

3.4.1 Inhibition of on-going responses (Stop Task)

As predicted, children with ADHD and children with TBI were found to suffer from a deficit in inhibitory control processes in the Stop Task in comparison to controls. Whereas children with TBI were slowed in both, the stop and the go-processes, ADHD children were only impaired in their stop-processes. This result is in line with the findings of Arcia and Gualtieri (1994) in ADD and mCHI adults. Interestingly, the scatterplot revealed that the slowing of the stop- and go-processes in the TBI group was uncorrelated, indicating that a general slowing was not responsible for the inhibitory control deficit. A basic assumption of Logan's race model is the independence of the stop and the go-process, and our findings also seem to underline that both processes can be differentially impaired (Logan, Cowan & Davis, 1984; Logan, 1994).

Although expected, no significant differences between TBI children with and without a secondary ADHD were found in the Stop Task. There was only a tendency for the TBI children with a postinjury ADHD symptomatology to have faster go-processes than TBI children without ADHD. There are several explanations for this finding: The result could suggest that the underlying mechanism for developmental ADHD and

secondary ADHD after TBI differ from each other: whereas developmental ADHD seems to be due to a deficit in inhibitory control processes indicated by longer SSRTs in the stop-task, postinjury ADHD may result from shorter go-processes measured by shorter MRTs. However, the activity data make another explanation more likely: in the TBI group without secondary ADHD a number of hypoactive children who suffered from a slowing in stop- and go- processes were present, whereas the children who were hyperactive according to the activity data showed the expected dissociation between stop- and go-processes. This finding needs, of course, a replication including a larger sample.

3.4.2 Inhibition on prepotent responses (Delay Task)

In contrast to the Stop Task, the results of the Delay Task were less consistent. No delay-dose-relationship was found, but only an impairment in inhibitory control for ADHD and TBI children in the long-delay-condition. This result is in line with Sonuga-Barke's model that ADHD arises from a deviant cognitive style characterized by a delay-aversion (Sonuga-Barke, Taylor & Sembi, 1992) and was extended to children with TBI in the present analysis. The result of a deficit in inhibition of prepotent reactions for TBI children has already been shown in Dennis' study with the Delay Task of the Gordon Diagnostic System (Dennis et al., 1995). Additionally, several studies reported deficits in prepotent response inhibition in children with ADHD (Iaboni et al., 1995; Sonuga-Barke et al., 1992).

A possible explanation for the normal performance of both clinical groups in the fast-speed-condition may be that the reward (shortening of and avoidance of delay) for an impulsive reaction (firing immediately at the UFO) was too weak in the short-delay-condition. Barkley (1997) has already suggested that it will prove difficult to document the inhibitory deficit within experimental settings in which rewards provided are relatively weak or no history of such reinforcements exists in the individual's experience. However, one also has to consider that the normal controls made more errors in the short-delay-condition, perhaps indicating that something other than inhibition has been measured, possibly perceptual acuity.

As was the case in the Stop Task, only the TBI children suffered from slower information processing, indicated by longer MRTs in both delay-conditions. TBI children with and without a secondary ADHD did not differ in inhibitory performance or in response speeds. Furthermore, the comparison of hypo-, normo-, and hyperactive TBIs

revealed poorer inhibitory performance in hyper- and hypoactive children. In addition, reaction times in hypoactive children were significantly longer in the long-delay-condition.

To summarize, in accordance with Barkley's model (1997) a pervasive inhibitory control deficit concerning prepotent (if delay is long enough) and on-going-responses inhibition was found in children with ADHD and TBI. There was no difference in the inhibitory performance of these two clinical groups, the TBI children, however, were also found to be slowed in their information processing speed. This observed slowing is in line with the literature on attention deficits after pediatric TBI (Dennis, Wilkinson & Koski, 1995; Cooley & Morris, 1990; McKay, Harlperin & Schwartz, 1994; Murray, Shum & McFarland, 1992).

3.4.3 Behavioral ratings versus activity measurement in TBI children

Forty-eight percent (n = 13) of the TBI children developed a secondary ADHD symptomatology according to the behavior ratings. This figure is in line with the recent literature, although there are also studies which indicate a lower prevalence (e.g., Brown, Chadwick & Shaffer, 1991). Closer to the present results, Max et al. (1997) found that in a sample of 50 children with TBI 56% fullfilled criteria for ADHD, including 10 children with ADHD symptoms prior to injury.

However, a poor correspondence was found between the activity data and the behavioral ratings through parents and staff in the TBI group (correlation between sum of hyperactive symptoms and total activity score: r = -.30), whereas the correspondence was at least satisfying for ADHD (r= .42) and control children (r = .38).

Only 6 of 13 TBI children who were rated as hyperactive by our interview and rating scale data were classified as hyperactive according to the actigraph data. The TBI children with ADHD consisted of 3 hypoactive, 4 normokinetic, and 6 hyperactive children, the TBI children without a secondary ADHD consisted of 6 hypoactive, 6 normokinetic and 2 hyperactive children. These figures indicate that the rating is biased by the fact that TBI children could also suffer from hypoactivity, a behavioral syndrome which was not included in the interview or the rating scales in the present study. Therefore, it seems to be important that further studies make use of rating scales including activity and impulsivity as dimensions with possible scoring on either "too much" or "too little". This seems to be especially important since the comparison of our TBI subdivisions revealed interesting patterns of deficits in stop- and go-processes despite the small sample sizes. According to the results of the "actigraph-corresponding" subgroup comparisons,

hyperactive TBI children show the same pattern of go- and stop-processes in the stop-task as children with developmental ADHD. Additionally, the results of the delayed-response task correspond well between children with developmental ADHD and hyperactive TBI children, indicating that poorer percentage of inhibition but average reaction times in the long-delay-condition seem to be characteristic of hyperactive symptoms. Interestingly, the hypoactive TBI children also suffered from an inhibitory deficit which was comparable to that of hyperactive TBI children. However, these children were additionally impaired in their information processing speed. Taken together, a slowing of the speed in the go-process seems to be a general consequence of TBI, which is not associated with any kind of behavioral disorder, whereas the slowing of the stop-process is always associated with either hypo- or hyperactivity after TBI.

3.5 CONCLUSION

Both ADHD and TBI children showed significant differences in two inhibition tasks compared to normal controls. Thus, the behavioral manifestations of both disorders not only share some degree of overlapping phenomenology, but also show similar underlying cognitive mechanisms, specified by an underlying inhibitory control deficit of prepotent and on-going responses. In addition, the TBI group suffered from a deficit in processing speed which seems to be independent of its inhibitory performance.

With regard to the results of the neuroimaging studies of children with developmental ADHD (Tannock, 1998) and the fact that frontal lobes are the most vulnerable regions for focal lesions in pediatric TBI (Levin & Kraus, 1994; Levin, Culhane & Mendelsohn, 1993), the inhibitory control deficit may be attributable to a frontal lobe dysfunction present in both groups.

However, the present experiment still cannot exclude the possibility that the poor inhibitory performance in children with TBI and children with ADHD overlaps only functionally, and not organically. Therefore, further research is needed to clarify the nature of this deficit. Illustrative of this type of research are the studies conducted by Tannock et al. (1989) and Tannock, Schachar and Logan (1995). These authors have shown that methylphenidate ameliorates not only behavior problems in children with developmental ADHD but also improves stopping by speeding up the inhibitory process. Interesting dissociations or correspondences between ADHD and TBI children in within-task

manipulations of inhibition tasks could help to clarify the nature of the inhibitory control deficit present in both groups.

Another unanswered question remains whether children with developmental or secondary ADHD after TBI suffer from a similar inhibitory control deficit. According to the subgroup analysis based on the behavior ratings the answer seems to be “no“; according to the subdivisions by the activity measurement the answer seems to be “yes“. Since the correspondence between activity measurement and behavior rating was especially low for the children with TBI, probably due to disregard of hypoactivity, the activity data seemed to be more reliable. Therefore, replication studies with larger sample sizes making use of neurobehavioral rating scales including hypoactive and abulic symptoms are needed.

4. LACK OF INHIBITION: A MOTIVATIONAL DEFICIT IN CHILDREN WITH ADHD AND CHILDREN WITH TBI?

4.1 INTRODUCTION

In the first study, it was shown that both, brain injured children and children with ADHD suffer from deficits in response inhibition (see also Anderson et al., 1998; Barkley, 1994; Dennis et al., 1995; Schachar et al., 1995). However, the precise nature of these inhibitory problems is still unknown. There are several models of inhibitory dysfunctions in children with developmental ADHD (for review see Barkley, 1997; Tannock, 1998), for example it is assumed that the inhibition deficit arises from a frontal lobe dysfunction (Pennington & Ozonoff, 1996), from an imbalance of the behavioral inhibition and behavioral activation system (Gray, 1982; Quay, 1988), from a deviant cognitive style characterized by delay-aversion (Sonuga-Barke, 1995) or from a dysfunction in effort (Sanders, 1983), whereas Barkley (1997) assumes response inhibition to be the primary deficit.

Although the models agree on the presence of an inhibitory control deficit in children with ADHD, they explain this deficit in different ways, make different assumptions about the underlying neural substrate of behavioral inhibition, and how much this deficit can be influenced by motivational factors (Barkley, 1997; Sonuga-Barke, 1995; Van der Meere, 1996). This latter point particularly has given rise to a controversy, primarily between those models that stress that these children are deficient in inhibitory

processes and those models that regard inhibitory problems as symptomatic of deviant motivational attitudes (Sonuga-Barke, 1995) or as dysfunctions in effort and activation components (Sergeant, 1996; Van der Meere, 1996). The motivational explanation of ADHD is supported by clinical evidence showing that ADHD symptomatology is affected by different situations, the presence of different persons, and is often not observable in novel situations (Sleator & Ullman, 1981) but develops gradually as more reinforcers modify behavior (Sagvolden, Metzger & Sagvolden, 1993). Additionally, empirical support comes from a series of studies which have shown that response contingencies enhance the performance of ADHD children in cognitive tasks (Corkum, Schachar & Siegel, 1996; Pelham, Milich & Walker, 1986; Van der Meere, Hughes, Börger & Sallee, 1995). Besides, recent studies have furnished further evidence for a shorter and steeper delay of reinforcement gradient, indicating that a reinforcer in close proximity to a response may be more effective in ADHD children than in normal controls (Sagvolden & Archer, 1989; Sagvolden, 1996; Sagvolden, Aase, Zeiner & Berger, 1998).

In contrast, no models exist to explain inhibitory control deficits in children with traumatic brain injuries (TBIs). However, following the ADHD literature, one may suggest a frontal lobe dysfunction to be responsible for the inhibition deficit, since the frontal lobe regions are the most vulnerable to focal lesions after TBI (Levin & Kraus, 1994; Levin et al., 1993). Assuming that structural brain damage causes the primary deficit in response inhibition, motivational factors may be considered as less important than in the etiological models for children with ADHD.

There is only one study which directly examines the effects of motivational influences on stopping behavior in children with developmental ADHD. Oosterlaan and Sergeant (1998) examined the effects of reward and response cost on response inhibition in 14 children with ADHD and found (contrary to their motivational hypothesis) that even in the presence of response contingencies, ADHD children showed poor response inhibition when compared to normal controls. However, the significance of this finding is limited by a small sample size as well as by a lack of any comparison to non-contingency-conditions.

In contrast, Jennings, Van der Molen, Pelham, Brock and Hoza (1997) found no differences between 11 children with ADHD and normal controls in performance of an inhibition task in which a motivating modification of the stop task was performed. Although the motivational hypotheses were not directly addressed in this study, a procedure was used, in which each successful inhibition was rewarded with a $ 0.05 bonus, whereas unsuccessful inhibition resulted in a $0.01 loss. Thus, the absence of performance

differences between ADHD and control children could be a result of the motivational modification of the stop-task.

To summarize, there are contradictory findings as to whether motivational factors are able to influence inhibition in children with ADHD and there are no studies dealing with this question directed at children with TBI, although both groups were shown to suffer from a response inhibition deficit. Therefore, the aim of this experiment was to investigate the influence of motivation on the stopping performance in children with ADHD and children with TBI. Assuming different underlying mechanisms for inhibitory control problems in children with developmental ADHD and children with TBI, it was hypothesize that reward contingencies may remedy poor response inhibition in children with ADHD whereas it may be ineffective at improving stopping behavior in children with TBI.

4.2 METHODS

4.2.1 Data analyzed in the present study

Data of 94 children were analyzed. Thirty-one children met DSM-IV criteria for ADHD and had no history of any brain injury, 37 children had suffered from a moderate to severe TBI, 26 were normal controls. Demographic features of the sample are presented in Table 4.1.

4.2.2 Reward contingencies

In the positive-reinforcement condition children earned credits for successful response inhibition in the Stop Task. Children received one point for each stop-signal trial in which they managed to inhibit their responses. During the intertrial interval feedback like („Good" „Super", „Go on like this") appeared on the computer screen and the child saw one point (symbolized by smilies) added to its credit. No feedback was provided if the children failed to inhibit. The children were told that the points served as tokens which could be exchanged for small presents (sweets, small toys, etc.) of their own choice at the end of the assessment. It was stressed that the number of tokens they could earn was dependent on their performance.

Reward was administered contingent on actual performance. Since the tracking procedure was used for measuring SSRT all subjects were able to inhibit approximately half of the stop-trials. Whereas under the no-reward condition six subjects failed to inhibit at

least 40% of the stop-signal trials, all children inhibited approximately 50% of the stop-signal trials in the reward-condition (M = 49,1%, Range from 46% to 53%). Therefore, the quantity of reward was equal for all subjects and problems due to different quantities of reward seem to have been excluded.

Each child was assessed twice, with a four-day-interval between first and second assessment. The experimental design made it impossible to vary the „no feedback"- and „positive feedback"-condition randomly, since children first reinforced would have suffered from a punishment condition, if no positive feedback had been provided on the second assessment. Therefore, the decision was made to measure the pure retest effect by examining a group of children twice without positive reinforcement on the day of the second assessment. Thus, on the second day, 10 children of each group were randomly assigned to the retest-condition, the remainder participated in the reinforcement condition.

4.2.3 Statistical analyses

Two separate (repeated measure x group) - ANOVAs were performed for the reward and retest-condition. A decision was made for two separate ANOVAs due to the unequal sample sizes of the repetition-condition compared to the reward condition. Critical alpha for the Pillais' spur statistics was set at 0.05. When a significant group difference emerged in this analysis, the effect was tested in pairwise comparisons between the groups. For post-hoc comparisons, the Tukey-HSD test at an alpha-level of .05 were used.

In addition, effect sizes (ω^2) were calculated separately for each group, in order to compare the influence of motivation and repetition for children with ADHD, TBI, and for normal controls.

4.3 RESULTS

Descriptive statistics in the inhibitory task performance for ADHD, TBI and control groups for the reinforcement and retest conditions are presented in Table 4.1. Sample sizes in the reinforcement condition were as follows: ADHD: n = 21, controls: n =16, TBI: n = 27, and in the retest condition: ADHD = TBI = controls: n = 10. To test for successful randomization, t-tests for independent groups were performed with SSRT and MRT of the first assessment as dependent variables. It was shown that there were no differences between the two conditions of each group (ranges of p between .2 and .9). All six subgroups were comparable with regard to age (p = .8) and IQ (p = .4).

Table 4.1.
Demographic features and descriptive statistics for inhibitory task performance of the sample separate for groups and conditions.

	TBI reward (n=27)	TBI repetition (n=10)	ADHD reward (n= 21)	ADHD repetition (n=10)	Controls reward (n=16)	Controls repetition (n=10)
	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)
Number of males	19	7	20	8	12	8
Age (years)	10.6 (1.7)	10.5 (1.2)	10.4 (1.6)	10.7 (1.3)	10.2 (1.3)	10.2 (1.1)
Raven-IQ	94 (14)	95 (12)	96 (14)	94 (12)	102 (14)	102 (12)
NCT (T-Value)	44 (15)	46 (14)	49 (9)	47 (8)	55 (12)	54 (12)
SSRT at 1st ass.	455 (113)	454 (115)	426 (68)	431 (62)	351 (68)	351 (70)
MRT at 1st ass.	706 (76)	730 (50)	621 (65)	593 (30)	573 (72)	572 (64)
SSRT at 2nd ass.	367 (85)	434 (116)	311 (51)	411 (63)	293 (58)	336 (72)
MRT at 2nd ass.	674 (90)	667 (61)	581 (80)	542 (30)	579 (70)	544 (60)

NCT = Number Connecting Test; SSRT at 1st ass. = stop signal reaction time at first assessment; SSRT at 2nd ass. = stop signal reaction time at second assessment; MRT at 1st ass. = mean go reaction time at first assessment; MRT at 2nd ass. = mean go reaction time at second assessment.

A 3 X 2 (Group X Time) repeated measure ANOVA for the reinforcement condition revealed a significant main effect for Time, $F(1, 61) = 102.2$, $p < 0.001$, and a significant Group X Time interaction, $F(2, 61) = 3.3$, $p = .045$, indicating that all children improved their performance under reinforcement, but that reward differentially affected SSRTs in the three groups. Post-hoc tests revealed that at the time of the first assessment, both, ADHD ($p = .03$) and TBI children ($p < .001$) showed longer SSRTs than the controls, but there was no significant difference between both clinical groups ($p = .5$) . However, under reinforcement conditions, ADHD and controls performed equally well ($p = .73$), but both differed significantly from the TBI group (ADHD < TBI, $p = .02$; controls < TBI, $p = .004$).

In contrast, in a further 3 X 2 (Group X Time) repeated measure ANOVA for the retest condition neither the Factor Time, $F(1, 27) = 2.4$, ns, nor the two-way-interaction between Group and Time, $F(2, 27) = 0.2$, ns, reached statistical significance. Thus, all three groups showed a comparable learning effect, but responded differentially to the reinforcement.

The interactions separated for group and conditions are depicted in Figure 4.1.

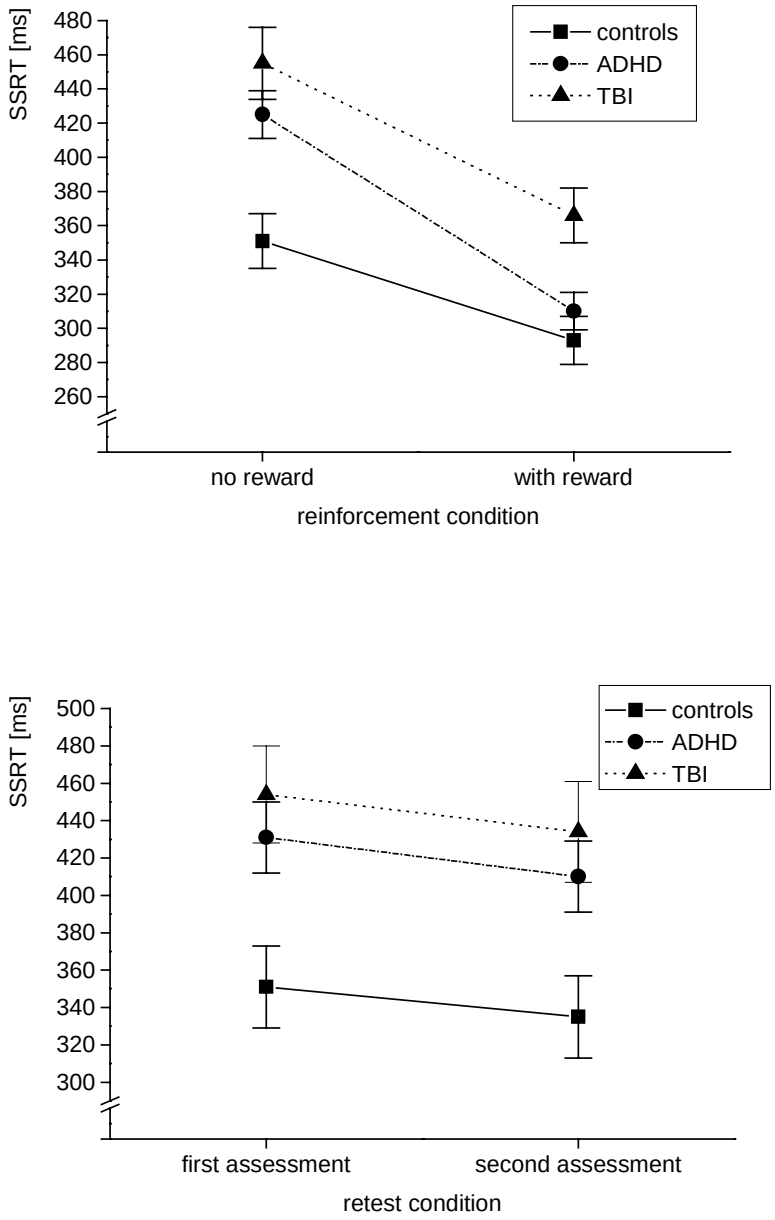

Figure 4.1. Stop Signal Reaction Time (SSRT) plotted by stop-task condition, separate for the reinforcement and retest condition.

In addition to this analysis the means of each quartile were calculated and plotted the four means for the first and second block of the reward condition. This procedure allows for a comparison of various parts of the SSRT distributions (Sanders & Hoogenboom, 1970). However, it has to be taken into account that the quartile values are not independent and the mean SSRTs present in one quartile are only a good indicator when the variance of these SSRTs is relatively small.

As can bee seen from Figure 4.2, there was a slight tendency for less improvement in the controls in the first quartile, indicating a small bottom effect. In addition, the decrease in SSRT was larger for initially slow TBI children, since the 4th quartile in the TBI group showed greater improvement than the other quartiles. However, in general, ADHD showed the largest decrease in SSRT and equal improvement was found for all four means.

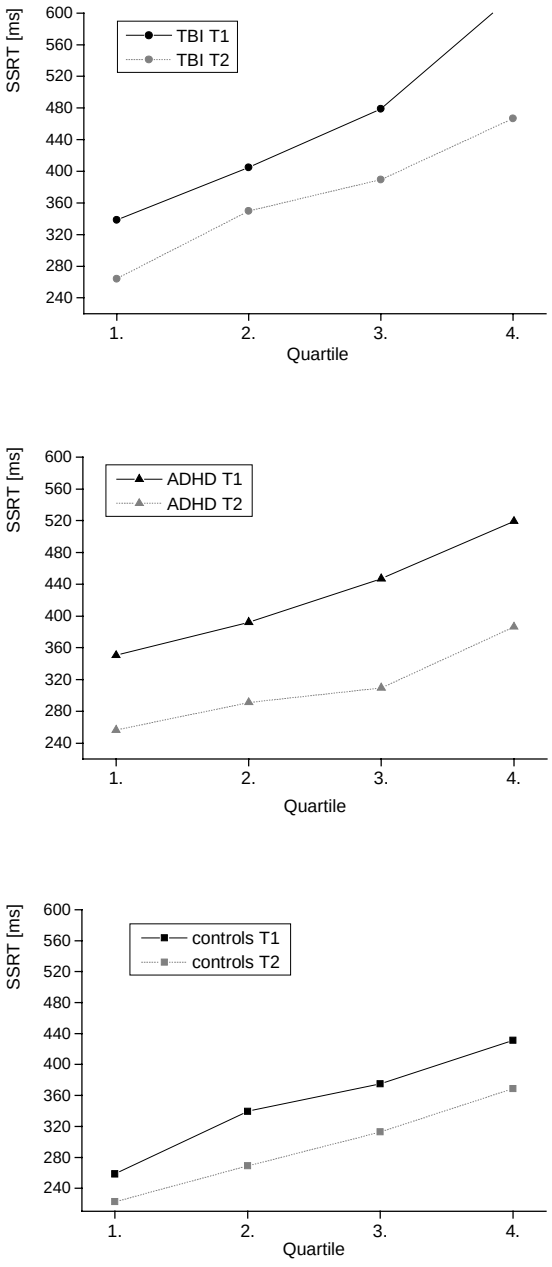

Figure 4.2. Stop Signal Reaction Time (SSRT) distribution with (T2) and without reward contingencies (T1) separate for each group.

4.3.1 Effect sizes

An overview of effect sizes for MRTs and SSRTs for all groups and conditions is presented in Table 4.3. Although there was no reinforcement condition for the Go-process in the present experiment, changes in MRT were controlled, since MRT may have changed in the second assessment due to indirect influences. For example, one could assume that children in the reward condition become generally aroused and therefore are also able to show faster responses (Kahneman, 1973).

Table 4.3.
Omega squared (ω^2) for SSRT and MRT separate for all groups and conditions.

Groups/ Conditions	SSRT ω^2	MRT ω^2
TBI/ reward (n = 27)	0.16	0.031
TBI/ repetition (n = 10)	- 0.0042	0.23
ADHD/ reward (n = 21)	0.47	0.05
ADHD/ repetition (n = 10)	0.016	0.26
Controls/ reward (n = 16)	0.17	- 0.006
Controls/ repetition (n = 10)	- 0.015	0.034

SSRT = stop signal reaction time; MRT = mean go reaction time.

The biggest effect size is found for SSRT in the ADHD group under reward conditions, whereas TBIs and controls demonstrated similar figures for treatment magnitude for SSRT improvement under reward conditions. The learning effect for stopping in the retest condition was poor in all groups, but interestingly both clinical groups speeded up their go-process in the retest condition.

However, since reward and repetition are confounded in this experiment, the effect of pure repetition has to be subtracted from the reward condition to achieve an estimate of the pure reward condition. Thus, the effect size for the pure reinforcement effect in the ADHD group would be about 0.45, which is still a large effect, according to Cohen (1977, pp. 284-288), indicating that reward accounted for a substantial amount of the variance of the speed of the inhibitory process. However, the assumed additivity can only be examined in further experiments.

4.4 DISCUSSION

The results of this study indicate that in general all children profit from reward and that this effect is larger than a simple repetition effect. This is in line with empirical findings on the effects of feedback and reward on performance (for a review, see Kluger & DeNisi, 1996). Nevertheless, the magnitude of this effects is astonishingly high (ES between .16 and .45), taking into account that stopping is considered as an automatic internally generated process, which was found to differ very little across strategies and tasks in previous studies (Logan, 1981; Logan & Cowan, 1984).

The results indicate that inhibitory deficits can be motivationally ameliorated (and performance becomes similar to that in normal controls) in children with ADHD. Children with TBI improved their inhibitory performance less than ADHD children in the reinforcement condition, although they showed a similar learning effect in the retest condition. The results differ from Oosterlaan's and Sergeant's study (1998) in which deficits in stopping were demonstrated in children with ADHD even under reward contingencies. However, the findings are concordant with the study of Jennings et al. (1997). There are several possible reasons for these observed discrepancies, one of them may be that gaining points may be a comparably weaker (and therefore less rewarding) contingency (as in Oosterlaan's study) than earning a small amount of money (as in Jennings' study) or changing points against small presents after the experimental session (as in the present study). Furthermore, in Oosterlaan's study, no baseline condition (without reward or response cost contingencies) was included and therefore the effects of reward and contingencies as such could not be determined.

The difference in stopping improvement between both clinical groups in this study may be interpreted in terms of different underlying mechanisms of inhibitory control deficits. The results in the ADHD group yield evidence for an underlying motivational deficit. This is in line with findings from previous studies, which have shown that performance in different cognitive tasks, such as the Continuous Performance Task (Corkum, Schachar & Siegel, 1996) or a learning experiment (Pelham, Milich & Walker, 1986) can be enhanced and normalized by response contingencies in children with ADHD, but has not been shown for the stop task before. As far as etiological models of ADHD are concerned, this finding is in favor of models that assume inhibitory control deficit as indicative of deviant motivational sets in children with ADHD (Sonuga-Barke, 1995; Sergeant, 1996; Van der Meere, 1996).

In contrast, poor response inhibition in the TBI group may be part of a general impairment in executive function which in turn may be attributable to a structural brain damage. This could possibly be a frontal lobe damage, although not necessarily, since Goldberg and Bilder (1987) have noted, that even in the absence of focal frontal contusions any diffuse brain dysfunction can disrupt what is considered to be executive function before other abilities are affected (see also Rabbitt, 1998). Further studies, including detailed analysis of the location of lesions and their relationship to inhibitory control deficits are needed to clarify this question.

However, an executive or frontal lobe dysfunction has also been suggested for children with ADHD as a cause for poor response inhibition (e.g., Pennington & Ozonoff, 1996; Barkley, 1994). This explanation is not incompatible with the present findings. Sagvolden and Sergeant (1998) suggest that according to recent studies there is no brain damage in children with ADHD but hypo-efficient dopamine systems. These give rise to neurochemical imbalances, causing behavioral problems as deficits in sustained attention, overactivity and impulsiveness. None of these symptoms are necessarily primary but may be secondary to an underlying deficit in reinforcement processes. The results of the present experiment support this view, since TBI (with brain damage) and ADHD (without a history of brain damage) respond differently to reward, indicating that alterations in reinforcement normalizes inhibitory control and impulsivity in children with ADHD but not in children with a structural brain damage. The present study does not examine the underlying mechanism of how reward changes the inhibitory performance in children with ADHD. One may assume that reward improves arousal and helps to normalize neurochemical alterations. Further research, including neuroimaging and neurobiochemical studies are necessary to clarify the way in which response contingencies affect children with ADHD.

4.4.1 The effects of methylphenidate compared to the effects of reward on stopping behavior in children with ADHD

A comparison of the effect sizes of the two studies by Tannock et al. (1989, 1995) that examined the influence of methylphenidate and the present study that examined reward contingencies, indicates a bigger treatment effect of reward contingencies than medication on stopping behavior for children with ADHD. The disadvantage of the present experiment is that in contrast to Tannock's study, repetition and reward are

confounded and one cannot be sure that the effects of both conditions are actually additive. However, the observed positive effect of reward is interesting with respect to therapeutic issues. It is in line with recent literature on empirically supported intervention approaches (for a review see Pelham & Hinshaw, 1992; Pelham, Wheeler & Chronis, 1998). For example, Pelham (1998) showed that in addition to pharmacological stimulant treatment only parent- or school-based contingency programs fulfill „task force criteria" for treatment in ADHD. Token economies in particular were found to be an effective treatment and tokens were also used in this experimental procedure.

5. CATECHOLAMINE ACTIVITY IN CHILDREN WITH TBI AND CHILDREN WITH ADHD

5.1 INTRODUCTION

While the acute neurobiochemical sequelae of traumatic brain injuries (TBI) are well described in the literature, little is known about the long-term neurobiochemical alterations or the relationship between chronic changes in the catecholamine systems and cognitive deficits or behavioral disturbances in brain injured children.

5.1.1 Initial catecholamine alterations after trauma

Initially in trauma, the local injury stimulates an inflammatory reaction that causes edema and depression of local metabolism (the ebb phase), but this is soon replaced by a generalized increased metabolism (the flow phase). TBI activates the sympathoadrenao-medullary axis, which contributes to systemic derangements such as increased intracranial pressure, cardiac arrhythmias and pulmonary complications (e.g., Clifton, Ziegler & Grossman, 1981). Plasma norepinephrine (NE) levels have been reported to be higher in patients with more severe brain injuries, determined by the Glasgow Coma Scale (GCS) than in patients with mild or moderate injury (Teasdale, 1981), whereas the degree of posttraumatic elevation of blood pressure and heart rate has been correlated with circulating NE concentrations (Clifton et al., 1981). Furthermore, it has been shown that circulating catecholamines, particularly NE, may be used as quantifiable markers to reflect the extent of brain injury and predict the likelihood of recovery (Woolf et al., 1987; Prasad et al., 1993). Correlation studies suggest that increases in circulating noradrenaline and

adrenaline are independently regulated (Frayn, 1986). According to a recent animal study those acute alterations which occur in regional concentrations of brain catecholamines following brain trauma, may persist even for prolonged periods (at least for one week for NE) postinjury (McIntosh, Yu & Gennarelli, 1994).

5.1.2 Chronic arousal changes in brain injured patients

Evidence for underarousal in brain injured children can only be derived from studies examining the efficiency of stimulant medication as well as from studies focussing on changes in autonomic responsivity after head injuries.

Several studies have provided evidence for the indication of stimulant medications, as methylphenidate or dextro amphetamines, in adults (Evans et al., 1987; Klove, 1987) and children with TBI (Hornyak, 1997). It was shown that administration of both stimulant medications improved cognitive functions, behavior and arousal, indicating that a change in the dopaminergic and norepinephrinergic system may be attributable to those cognitive and behavioral disturbances after TBI.

Central arousal impairments might be also reflective in decreased measures of skin conductance responsitivity, since this measure has been shown to correlate well with more direct indices of cortical activation such as EEG desynchronization and presumably reflects a direct influence of the brain stem reticular activating system on autonomic sympathetic activity. Therefore, studies applying skin conductance responsitivity to brain injured patients may be of further interest.

Randolph, Miller, Towner and Pollack (1992) examined the skin conductance levels and responsitivity in a group of 15 patients recovering from closed head injuries with 15 matched controls. Measurements were taken during rest periods and two activation periods, consisting of a series of 80 dB tones and a cognitive task. Patients exhibited significantly lower levels of skin conductance and significantly fewer responses than the control group. Also the group by task interactions were significant, indicating that the control group was much more responsive during both activation periods. However, since skin conductance responsitivity in the patient group was not found to be associated with duration of posttraumatic amnesia, behavioral disturbances following CHI may have been coincidental.

A similar study was performed by Andersson and Finset (1998). Autonomic reactivity in response to two mentally challenging tasks was studied in 33 patients with traumatic brain injury (TBI), 27 patients with cerebrovascular insults (CVA), and 14

patients with hypoxic brain damage. Heart rate, skin conductance level, and number of spontaneous skin conductance responses were recorded during baseline and two problem-solving stress conditions consisting of Raven Progressive Matrices and mental arithmetic. CVA and TBI patients with focal right hemisphere injury showed significantly reduced stress reactivity compared to patients with focal left hemisphere injury. This right-left hemisphere difference was maintained when controlled for diagnosis, gender, sex, age, and stressor task performance and involvement. The results indicated that lateralization of lesion rather than diagnosis or etiology was the critical factor in autonomic stress hyporeactivity in brain-injured patients.

5.1.3 Epinephrine and norepinephrine excretion in children with ADHD

Previous research has provided support for the involvement of dopamine (DA) and norepinephrine (NE) in the pathophysiology of Attention-Deficit Hyperactivity Disorder (ADHD). Zametkin and Rapoport (1986) argued that no single transmitter is exclusively involved in the pathology of ADHD, both because stimulant medications always affect more than one neurotransmitter and because of the multiple interrelations among specific catecholamines and their precursors and metabolites. They argue that the combined action of dopaminergic and noradrenergic systems should be considered in the biology of ADHD (see also Oades, 1987). Whereas dopamine seems to be especially involved in the presence of hyperactivity, the locus coeruleus which consists primarily of noradrenergic neurons plays a major role in attention (Aston-Jones et al., 1984).

Clinical studies of homovanillic acid (HVA), the principal metabolite of dopamine in cerebrospinal fluid (CSF) and urine, did not yield data consistent with the dopamine deficiency hypothesis of ADHD. CSF HVA did not differ between normal controls, aggressive children, and ADHD children (Castellanos, Elia et al., 1994). In addition, no relationship was found with laboratory measures of either aggression or impulsivity (Kruesi et al., 1994). A pharmacological treatment with L-Dopa or several dopamine agonists did not show significant improvement in the behavior of ADHD children. Thus, it seems unlikely that ADHD is related to a simple hypofunctioning of the dopamine system. It might be important to know that there are at least five dopamine receptors known (Solanto, 2000), which respond differently to dopamine agonists and antagonists. For instance, Sawaguchi and Goldman-Rakic (1991) have shown that while D1 antagonists disrupt working memory in nonhuman primates, D2 antagonists show little effect, raising

the possibility that only the D1 receptor is critical for this function. Solanto (1984; 1986) reviewed animal studies in which dopamine or apomorphine (a dopamine agonist) was applied iontophoretically in the substantia nigra or nucleus accumbens. Low doses of dopamine agonists were found to preferentially stimulate the presynaptic autoreceptor, while higher doses were necessary to stimulate postsynatpic dopamine receptors (Sokol et al., 1987). Solanto (1984) suggested that stimulants in low doses might stimulate dopamine autoreceptors, leading to decreased dopamine release. Indeed, low doses of apomorphine decrease activity in rodents. Solanto (1984) hypothesized that stimulants exert their therapeutic effects by the stimulation of dopamine autoreceptors. In an experimental test of this hypothesis, Solanto (1986) performed a double-blind, placebo-controlled trial of a very low dose of methylphenidate (0. 1 mg/kg). Such low doses are more likely to stimulate only dopamine autoreceptors as in the animal studies above. These low doses were effective in reducing activity levels in children with ADHD, but they did not improve attention as measured by a laboratory task. The hyperdopaminergic state in the ventral striatum might account for a part of the symptomatology, namely the hyperactivity in ADHD.

Early empirical studies concerning the norepinephrinergic system were characterized by methodological problems and contradictory findings. For example, all studies using 24-hour urine samples reported heterogeneous findings. Thus, two studies found that ADHD children showed lower excretion of 3-Methoxy-4-Hydroxyphenylglycol (MHPG) (Shekim et al., 1977; 1979; 1983; Yu-cun & Yu-feng, 1984), whereas this could not be replicated by three further studies (Khan & Dekirmenjian, 1981; Rapaport et al., 1978; Wender et al., 1971).

The pharmacological findings for a norephinephrinergic dysfunction in ADHD are generally unclear. On the one hand, it was shown that d-amphetamine caused a decreased excretion of MHPG, which was also positively correlated with a clinical improvement in ADHD symptoms (Yu-cun & Yu-feng, 1984), on the other hand no MHPG reduction was observed during medication with methylphenidate. On the contrary, methylphenidate even seemed to trigger a global increase in norepinephrine excretion (Solanto, 2000).

5.1.4 Catecholamine activity during cognitive stress

In their recent review on catecholamines in ADHD, Pliszka et al. (1996) state that the data clearly indicate that all three neurotransmitters, epinephrine (EPI), norepinphrine

(NE) as well as dopamine (DA) are involved in the pathophysiology of ADHD, but hypotheses suggesting ”too much” or ”too little” of a single neurotransmitter no longer suffice.

There is more evidence for a multistage hypothesis which emphasizes the interaction of norepinephrine, epinephrine, and dopamine in the modulation of attention and impulse control. This model assumes that the central norepinephrine system may be dysregulated in ADHD, such that this system does not efficiently ”prime” the cortical posterior attention system to external stimuli. Effective mental processing of information involves an anterior executive attention system which may depend on dopaminergic input (Pliszka et al., 1996). The peripheral epinephrine system may be a critical factor in the response of individuals with ADHD to stimulant medication. For example, Brown et al. (1980) as well as Coons et al. (1987) showed that only children who had an increased catecholamine excretion after stimulant medication showed an improvement in their information processing and in ADHD symptoms.

In his review, Dienstbier (1989) summarized that stress tolerance and good performance on tasks were related both to low basal levels of catecholamines and to higher acute releases of catecholamine during mental stress. This clearly suggests that it is necessary to examine the dynamics of catecholamine release in response to events rather than the static baseline level of catecholamine. Therefore, studies examining the urinary excretion of norepinephrine during cognitive tasks in children with ADHD are of special interest.

For example, healthy children who showed a higher adrenaline excretion during school lessons were rated as less aggressive and restless by their teachers as well as better emotionally and socially adjusted (Frankenhaeuser & Johansson, 1975). Elwood et al. (1986) found that children who showed increases in urinary EPI during a stressor situation demonstrated improved selective attention and less deterioration in sustained attention.

Of special interest are two studies, both of them examined the catecholamine excretion in children with ADHD during cognitive tasks (Pliszka et al., 1994; Hanna, Ornitz & Hariharan, 1996). Pliszka et al (1994) tested whether there are differences in noradrenergic or adrenergic functioning in children with attention-deficit hyperactivity disorder (ADHD) with and without anxiety. Therefore, ADHD children with and without a comorbid overanxious (ANX) disorder were compared to each other and to normal controls in terms of 2-hour urinary excretion of norepinephrine, epinephrine, and their metabolites. All subjects performed a fixed series of mentally stressful tasks during the

collection period. It was demonstrated that children with ADHD, regardless of comorbid anxiety, excreted more normetanephrine (NMN), the chief extracellular metabolite of NE than controls as well as more vanillylmandelic acid. This was interpreted as evidence that ADHD children have a higher tonic release of norepinephrine. It was shown that children with ADHD alone had lower NE/NMN and EPI/metanephrine ratios compared to controls indicating that they also have a decreased pulsatile excretion of catecholamines. This is concordant with the results of a study by Klinteberg and Magnusson (1989) who reported that a lower reactivity of the sympathic nervous system to external stress is a risk factor for hyperactivity.

A very similar study was performed by Hanna et al. (1996). They examined the urinary catecholamine excretion in 16 boys with ADHD and 12 normal controls in response to a standardized intelligence test. They found urinary EPI-excretion after the mentally stressful task to be 40% lower in ADHD children compared to the control group.

However, it has to be noted that both studies suffer from a missing baseline test and thus fail to show that both groups did not differ in ”resting catecholamine excretion”.

5.1.5 Spontaneous eye blink rate as an indirect measure of central dopaminergic activity in pediatric patients

Although decreased blink rates have been successfully demonstrated in hypodopaminergic states, Daugherty, Quay, and Ramos (1993) found no significant differences in the blink rate between unmedicated children with ADHD, ADHD plus conduct disorder, and normal controls during conversation. Caplan, Guthrie and Komo (1996) examined the spontaneous eyeblinking in 28 children with ADHD and 47 normal controls during a listening, a conversation, and a verbal recall task. Unlike the normal children, children with ADHD did not increase their eyeblink rates significantly across these three tasks. The ADHD subjects who were not on stimulant medication had significantly lower eyeblink rates than the normal children during the verbal recall condition. The ADHD subjects on stimulants, however, had significantly higher blink rates than the normal subjects during the listening task. Taken together, it remains unclear, whether children with ADHD suffer from a decreased blink rate in general or if they are only unable to modulate their blink rates across different cognitive tasks.

The central dopaminergic functioning has not been studied in subjects with TBI yet, however, Vreugdenhil et al. (1997) found in 50 children with acquired

immunodeficiency syndrome (AIDS) that higher blink rates in these children were associated with more severe cortical atrophy and white matter abnormality on computed tomographic brain scans, whereas the presence or severity of basal ganglia calcifications did not seem to influence blink rate. In addition, higher blink rates were associated with higher ratings of depressed affect and lower ratings of hyperactive behaviors.

5.1.6 Summary and aim of this study

Despite the functional similarities between children with TBI and children with ADHD and despite the empirical findings for pharmacological stimulant treatment effective in both groups, no studies exist that examined catecholamine functioning in children with chronic TBI. Previous research has provided evidence for initial changes in catecholamine excretion after trauma as well as for long term impairments in arousal in brain injured adult patients. Additionally, children with ADHD were found to suffer from alterations in phasic activation of the norepinephrine and epinephrine system as well as from a hypofunctioning of the dopaminergic system.

The aim of this study was to come to a better understanding of the long-term neurobiochemical sequelae after traumatic brain injury in children, by comparing the catecholamine excretion of the norepinephrine and epinephrine system before and after cognitive stress in children with TBI, children with developmental ADHD, and normal controls. According to Pliszka's (1994) and Hanna's (1996) results, it was hypothesized that children with ADHD may show a decreased pulsatile excretion of catecholamines, indicated by lower levels of EPI post-stress as well as a higher release of NMN pre-stress compared to normal controls due to a higher tonic activation of the noradrenergic system.

For children with TBI, a similar change in the phasic activation system of the norepinephrine and epinephrine systeme was assumed. However, based on Randolph's results (1992) concerning the decreased autonomic responsitivity in the resting situation in adult patients with CHI it was hypothesized that children with TBI may additionally show tonic alterations in their EPI excretion in the resting situation in comparison to healthy controls. Furthermore, as TBI children with a more severe trauma, measured by the GCS scores were found to show larger initial changes in the norepinephrine system after trauma (e.g., Prasad et al., 1993), also higher alterations of catecholamine excretion in both the resting and stressful situation were assumed for the more severely injured TBI children.

In addition, as predicted from theories of dopamine function in ADHD, it was expected that children with ADHD may show a decreased eyeblink rate compared to

normal controls in a task with high cognitive demands. A change in the eyeblink rate in children with TBI was also hypothesized, but it was not stated in which direction.

5.2 METHODS

5.2.1 Data analyzed in the present study

Data of 84 children were available for the present exploratory analysis. Thirty-one children met DSM-IV criteria for ADHD and had no history of any brain injury, 27 children had suffered from a moderate to severe TBI, 26 were normal controls.

In the TBI group, data of severity of trauma, measured with the Glasgow Coma Scale (GCS) within the first 24-h postinjury, were derived from the patients' medical records, but were only obtainable in 17 children. According to these data 9 children suffered from a severe, 8 children from a moderate TBI. The demographic and clinical features of all three groups are described in Table 5.1.

Table 5.1.
Descriptive statistics and frequency of comorbid diagnosis in Children with TBI, with ADHD, and normal controls.

	Groups		
	TBI (n=27)	ADHD (n= 31)	Controls (n=26)
	M (SD)	M (SD)	M (SD)
Age at testing (years)	10.6 (1.7)	10.5 (1.6)	10.2 (1.2)
Raven-IQ	91 (14)	95 (13)	102 (13)
Number Connecting Test (T-Value)	43 (15)	48 (8)	58 (12)
Total score of activity (per hour) [a]	3625 (2519)	5203 (2293)	3611 (1772)
	n	n	n
Number of males	19	28	20
Anxiety Disorders	4	11	3
ODD, CD	8	11	1
sADHD [b]	13		

[a] Arbitrary units, [b] secondary ADHD

5.2.2 High-pressure liquid chromatography (HPLC)

The HPLC hardware consisted of a Waters (Eschborn, Germany) Model 510 pump, a Waters 712 plus autosampler and a Waters 460 electrochemical detector. A Waters Resolve 5 µ spherical C_{18} column (3.9 x 150 mm, part no. 85711) was used to measure

norepinephrine (NE), epinephrine (EPI) and dopamine (DA), while the Chromsystems (Martinsried, Germany) analytical columns order no. 1100/B or order no. 2100 were employed for measurement of vanillylmandelic acid (VMA) and homovanillic acid (HVA) or normetanephrine (NMN) and metanephrine (MN), respectively.

Commercial reagent kits for sample preparation and HPLC-analysis of VMA, HVA and MN, NMN (containing mobile phase, calibration standards, internal standards, washing buffers, elution buffer and sample clean up columns) were purchased from Chromsystems (order no. 1000/B and order no. 2000, respectively). The injection volume was 15 – 20 µl, the flow rate 0.9 – 1.3 ml/min depending on the age of the column and the detection potential +760 mV (VMA, HVA) or +750 mV (MN, NMN).

To 5 ml of acidified urine 50 µl internal standard (72 µM 3,4-Dihydroxybenzylamine [Sigma, Deisenhofen, Germany, product no. 85,878-1] in 1 % HCl [v/v]) and 15 ml 0.1 % EDTA (w/v) were added. After adjusting the pH to 6.45 with 0.5 M NaOH the mixture was loaded onto disposable cation exchange resin columns (Biorad, Witten, Germany, order no. 195 6012). Then, the columns were washed twice with 5 ml of HPLC-grade water. Elution with 8 ml of 4 % boric acid (w/v) (Merck, Darmstadt, Germany, order no. 100765) followed and 15 – 20 µl of the eluate were injected into the HPLC system (mobile phase from chromsystems, order no. 5001, flow rate 0.9 – 1.3 ml/min, detection potential +600 mV). Calibration was performed with the calibration standard catecholamines from Biorad (order no. 1956021).

HPLC results were expressed as creatinine ratios as recommended by Tuchman et al. (1985). Creatinine was measured in acidified urine with a kinetic colorimetric assay (HiCo Creatinine Jaffé method without deproteinization, rate-blanked and compensated) using an automated Boehringer Mannheim/Hitachi 917 clinical chemistry analyzer. It was verified by parallel measurements of 55 pairs of either acidified or non-acidified urine samples that the acidification of the samples did not have any influence on the validity of the creatinine results.

5.2.3 Spontaneous eyeblink rate

Children were videotaped with a super-vhs-camera during the whole procedure. Using a zoom-in feature, the videocamera focuses on the child's face throughout the testing. The eyeblink rate was measured during a five-minute waiting period at the end of the examination after the urine sampling was finished and before the children got a certificate that they participated in the study. Two independent raters with no knowledge

about the children's diagnosis, counted the spontaneous blinking over the intermediate three minutes of those five minutes waiting. Interrater reliability between the two observers was .98, indicating that eye blinks were reliably counted. The mean of the two observers counts was used for calculating the mean blinks per minute for each subjects. Children with a blinking tic were excluded from the analysis (2 children in the ADHD group, 1 child in the TBI group and 2 children in the control group excluded).

5.2.4 Procedures

The assessment lasted about 90 minutes and all procedures were completed between 9.00 and 12.00 hours to exclude circadian differences in catecholamine release. Parents were instructed to give their children no caffeine or chocolates for breakfast on the morning of the urinary catecholamine sampling. None of the children in the ADHD or control group received any kind of medication for at least 4 weeks before the urinary catecholamine sampling. However, in the TBI group there were four children on anticonvulsant medication.

The first urine sample was collected before the assessment started in a resting situation. It was made sure that this sample was not the morning urine, but the second urine of the day. After the children had urinated, they were told to drink 100 mL of water before the attention tasks were performed. The post-sample was collected after the 90 minutes lasting assessment.

After collection, all urine samples were acidified immediately to pH 2 – 3 with 25 % (v/v) HCl, placed on ice and stored in 2 – 5 ml aliquots at – 80 °C in the dark. At the time of the assay, the samples were thawed at room temperature and analyzed blind to study group status.

5.2.5 Statistical analyses

A multivariate 3 X 2 (Group X Time) repeated measure analysis of variance (MANOVA) was conducted to analyze the catecholamine data. Between subject factor was Group (TBI, ADHD, controls), within subject factor was Time (pre vs. post cognitive stress), dependant variables were EPI, NE, M and NMN excretion. In addition, a separate ANOVA was calculated for the eyeblink rate data. Tukey's studentized range (HSD) post hoc analyses were employed to investigate possible group differences.

Furthermore, Pearson product-moment correlations were used to examine the relationship between behavioral measures and catecholamine data/ eyeblink rate in all

children as well as for the relationship between injury severity and catecholamine data/ eyeblink rate in the TBI group.

5.3 RESULTS

5.3.1 Catecholamine excretion and eyeblink rate

First, gender and comorbidity-differences were tested separately for each group. No significant differences were found. Pre and post-stress excretion of EPI, NE, MN, NMN for children with ADHD, TBI and normal controls are described in Table 5.2. All catecholamine data were related on the child's creatinine excretion, as described above, and expressed as 10^{-2} [mg/ml] units. In addition, group means and standard deviations of the eyeblink rate data are shown in Table 5.2.

Table 5.2.
Urinary catecholamines related on creatinine in 10^{-2} [mg/ml] and the spontaneous eyeblink rate (per minute) in children with TBI, with ADHD and normal controls.

	Groups			
	TBI (n=27)	ADHD (n= 31)	Controls (n=26)	univariate ANOVA
	M (SD)	M (SD)	M (SD)	p
Pre-stress:				
EPI	5.03 (2.76)	4.15 (2.57)	3.56 (1.65)	.086
MN	94.88 (44.63)	72.48 (27.36)	65.31 (26.14)	.005
NE	30.03 (14.97)	26.10 (10.47)	24.46 (9.49)	ns
NMN	174.20 (40.45)	175.91 (52.48)	140.68 (45.85)	.010
Ratios:				
EPI/ MN	6.29 (4.75)	6.49 (4.69)	6.66 (5.64)	ns
NE/ NMN	17.90 (10.41)	16.65 (10.58)	18.78 (9.56)	ns
Post-stress:				
EPI	6.09 (3.42)	5.88 (2.93)	10.56 (3.52)	.000
MN	94.18 (27.46)	67.94 (35.88)	94.38 (27.21)	.010
NE	36.56 (14.09)	28.32 (8.52)	35.76 (15.53)	.027
NMN	210.31 (98.05)	162.14 (61.18)	181.41 (65.57)	.058
Ratios:				
EPI/ MN	7.02 (5.32)	13.85 (16.01)	14.21 (7.54)	.030
NE/ NMN	19.16 (7.02)	19.93 (10.35)	21.45 (12.26)	ns
Eyeblink rate (per minute)	10.3 (4.3)	9.23 (3.1)	12.39 (4.5)	.01

EPI = Epinephrine; MN = Metanephrine; NE = Norepinephrine; NMN = Normetanephrine.

The multivariate MANOVA for the catecholamine data revealed significant main effects for Group ($F(8, 160) = 4.03$, $p < .001$), Time ($F(4, 79) = 23.96$, $p < .001$) and the Group X Time interaction ($F(8, 158) = 8{,}26$, $p < .001$). The following univariate ANOVAs showed significant Time effects for epinephrine ($F(1, 82) = 90.3$, $p < .001$), norepinephrine ($F(1, 82) = 21.56$, $p < .001$) and normetanephrine ($F(1, 82) = 8.9$, $p < .004$), but no differences in metanephrine excretion ($F(1, 82) = 1.4$, ns). Significant group effects were found for the epinephrine system (EPI: $F(1, 82) = 5.5$, $p < .006$; M: $F(1, 82) = 6.4$, $p < .003$), but only tendencies for the norepinephrinergic activity (NE: $F(1, 82) = 2.5$, $p < .09$; NMN: $F(1, 82) = 2.41$, $p < .09$). However, all Group X Time interactions reached statistical significance (EPI: $F(2, 82) = 28.6$, $p < .001$; NE: $F(2, 82) = 3.4$, $p < .04$; M: $F(2, 82) = 3.3$, $p < .05$; NMN: $F(2, 82) = 6.5$, $p < .002$). Tukey's studentized range (HSD) post-hoc procedures revealed that the TBI group tended to have a higher epinephrine excretion pre-stress ($p = .073$) compared to normal controls and also demonstrated a significantly higher release of M pre-stress compared to children with ADHD and normal controls (TBI > ADHD: $p = .03$; TBI > controls: $p = .005$) indicating a higher tonic activity of the epinephrinergic system for children with TBI. For norepinephrinergic activity pre-stress, no significant group differences were found for NE excretion. However, both clinical groups showed a significantly higher excretion of its main metabolite NMN, illustrating that both, children with TBI and children with ADHD suffer from a higher tonic activation of the norepinephrinergic system (TBI > controls: $p = .03$; ADHD > controls: $p = .02$).

The post-hoc procedures for the post-stress catecholamine data revealed a significantly higher release of EPI post-stress for the healthy controls compared to children with ADHD ($p < .001$) and children with TBI ($p < .001$). However, the TBI group also showed a higher M excretion compared to ADHD children (TBI > ADHD: $p = .01$) and the controls tended to excrete more M post-stress than children with ADHD ($p = .09$). Since the TBI children did not show a pulsatile release of EPI, the higher amount of M post-stress seemed to be due to their higher tonic activation of the epinephrinergic systems, whereas in the control group the tendency of a higher excretion can be related to their pulsatile release of EPI. For the norepinephrinergic activity post-stress, it was found that children with TBI and normal controls showed a slightly higher release of NE than children with ADHD (TBI > ADHD: $p = .04$, Controls > ADHD: $p = .07$). Again, the NMN excretion post-stress differed only between children with TBI and children with ADHD (TBI > ADHD: $p = .04$).

In Figure 5.1 the group x time interactions are visualized.

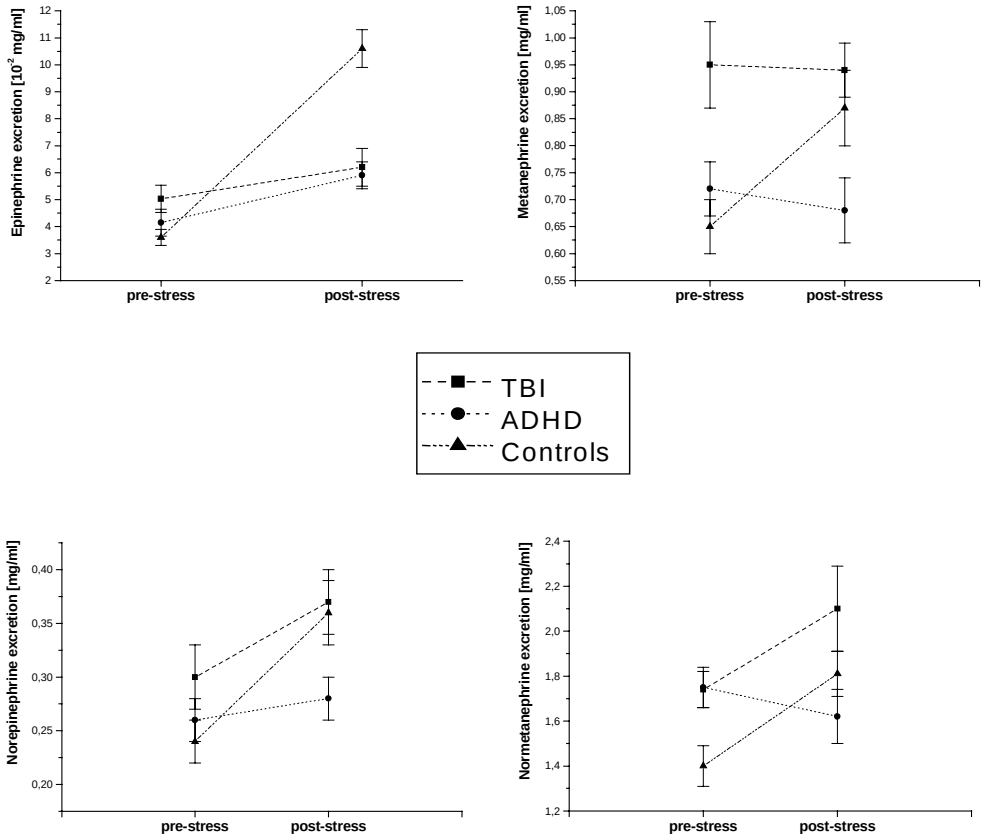

Figure 5.1. Means and standard errors of epinephrine, metanephrine, norepinephrine and normetanephrine excretion before and after cognitive stress, separate for children with TBI, ADHD, and normal controls.

In addition, the percentages of change in excretion of catecholamines and their metabolites are illustrated in Figure 5.2. As is shown, group differences in change of excretion are larger for the epinephrinergic system compared to the norepinephrinergic system.

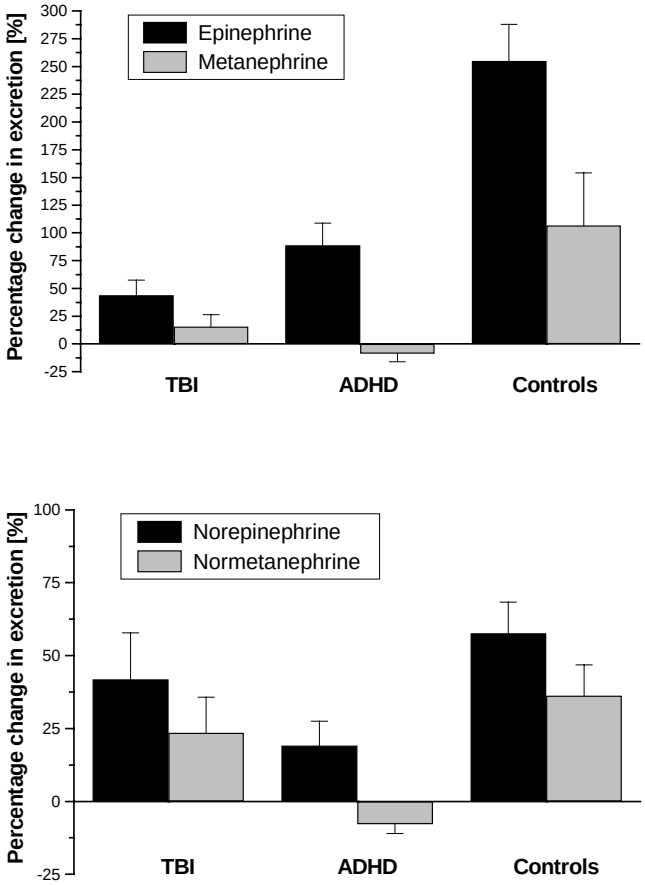

Figure 5.2. Mean and standard error of the percentage of change in excretion of catecholamines and their metabolites separately for children with TBI, ADHD and normal controls.

The ANOVA statistics for the eyeblink rate demonstrated a significant main effect for group ($F(2, 77) = 4.5$, $p<.01$). Tukey's studentized range (HSD) tests showed that both clinical groups had a significant lower eye blink rate (ADHD < controls: $p < .02$; TBI < controls: $p < .05$), whereas there was no significant difference between children with ADHD and children with TBI.

5.3.2 Relationships among behavioral and cognitive measures and catecholamine data

Table 5.3 shows the results of the Pearson product-moment correlations of the catecholamine data with cognitive and behavioral measures for all subjects. Moderately high negative correlations were found for either the number of inattentive or hyperactive-impulsive symptoms and EPI excretion post-stress, indicating that the more ADHD

symptoms the lower the EPI excretion after cognitive stress. Besides, moderately high positive correlations were observed between noradrenergic pre-stress activity and the actigraph data, as well as between the eyeblink rate and the T-Value in the Number Connecting Test, which measures cognitive speed.

Table 5.3. Correlations of catecholamine data with behavioral and cognitive measures.

	Cognitive and behavioral measures					
Catecholamine Data	in	hi	IQ	MRT	NCT	activity
EPI pre	.16	-.08	.17	.14	-.14	.02
EPI post	-.33 *	-.30 *	.13	-.27	.28	.05
M pre	-.003	-.09	-.14	.15	-.30	-.18
M post	-.25	-.21	.11	.06	-.05	.25
NE pre	.19	.04	-.10	.03	-.005	.35 *
NE post	.-20	-.27	-.11	.12	.04	.07
NMN pre	.12	.08	.05	.15	-.30	-.29
NMN post	-.13	-.10	.19	.18	-.16	.06
Eyeblink rate	-.16	-.06	-.006	-.13	.45 *	.04

Note: in = number of inattentive symptoms; hi = number of hyperactive-impulsive symptoms; IQ = Raven-IQ; MRT = primary reaction time in a two-choice reaction time task; NCT = Number Connecting Test (T-value), activity = actigraph activity (total score per hour), EPI = Epinephrine; MN = Metanephrine; NE = Norepinephrine; NMN = Normetanephrine.
* $p < .01$.

Correlations among severity of TBI measured by the GCS and catecholamine data as well as among anticonvulsant medication and catecholamine data were calculated, but no significant correlations, neither for the urinary data nor for eyeblink rate, were found.

5.4 DISCUSSION

5.4.1 Norepinephrinergic system

As predicted, children with ADHD were found to suffer from a deficit in their pulsatile excretion of EPI after cognitive stress. This finding replicates the results of the studies by Hanna et al. (1996) and Pliszka et al. (1994). Furthermore, our results add further knowledge to the current debate whether ADHD is associated with insufficient or excessive catecholamine receptor stimulation, since either insufficient or excessive catecholamine receptor stimulation can cause prefrontal cortex dysfunction (for review see Arnsten, 1998). According to the results of the present study, ADHD children seem to suffer from a tonic overactivation of the NE system, indicated by higher release of NMN in the pre-stress condition and an additional impairment in adapting their EPI excretion to

stressful events, indicated by lower levels of EPI post-stress. One could assume that the excessive NE release at central synapses might lead to excessive inhibition of cortical activity and the loss of the ability of locus coereleus (LC) to enhance the signal-to-noise ratio for incoming stimuli, resulting in attentional deficits as disengaging from old stimuli, or shifting attention to new data (see also Pliszka et al., 1996). Additionally, the impaired rise in EPI excretion in response to cognitive stress might impact on the locus coeruleus and prevent the feedback from the periphery. This might lead to excessive tonic activity of the LC and the peripheral sympathetic system.

The present results are in line with findings that noradrenergic agents are effective in treating ADHD in addition to pharmacological agents that increase DA transmission. These include the noradrenergic antidepressant desipramine or the new selective NE reuptake blocker, tomoxetine (Wilens, 1996; Spencer, 1998). Several studies have shown that some DA agents, such as methylphenidate and dextramphetamine increase urinary EPI (Elia et al., 1990), indicating a close interaction of the DA and NE systems and the rise in peripheral EPI as a critical factor for stimulant response in children with ADHD.

In contrast to the results by Pliszka et al. (1994), differences between ADHD children with and without a comorbid diagnosis of anxiety were not significant. This may be due to a smaller sample size of anxious children in the present study. Although some studies suggest that females with ADHD tend to show greater brain metabolism abnormalities than males (Ernst et al., 1994; Zametkin et al., 1993) gender-related differences were not present in this study which may be again due to the small number of females.

For children with TBI, a similar phasic deficiency in EPI excretion after cognitive stress was found as in children with ADHD. However, an important difference in catecholamine activity between children with TBI and children with ADHD was that the TBI group also suffered from a higher tonic activation of the EPI system, demonstrated by higher M excretion before cognitive stress. Also Randolph's finding (1992) of a decreased skin conductance in adults with closed head injuries in a resting situation suggests a chronic overactivation of the autonomic nervous system resulting in decreased skin conductance in brain injured patients.

The catecholamine changes in the TBI group were not correlated with the severity of trauma, a result which makes a relationship between a damage in the brain stem reticular activation system and the biochemical underarousal unlikely. This is in line with Randolph's study (1992) which has also found that skin conductance responsitivity in a CHI patient

group was not associated with the severity of trauma, measured by the duration of the posttraumatic amnesia. However, this finding is contradictory to results of studies examining the initial catecholamine changes after TBI, indicating that acute and chronic changes in catecholamine excretion may be influenced by different mechanisms. For the investigation of the longterm development of catecholamine alterations after TBI, longitudinal studies may be of special interest.

5.4.2 Dopaminergic system

The method to measure the spontaneous eyeblink rate in the current study seems to be valid and reliable. The interrater reliabilities were acceptable. Moreover, the data replicated a number of common characteristics of blink rate, e.g., the blink rates of normal controls were comparable to previously published rates in normal children (e.g., Zametkin et al., 1979) and a comparable increase with age was found ($r = .20$, $p = .08$).

In the present study, blink rate was measured while subjects were waiting for the end of the examination. As predicted, a significantly decreased blink rate in unmedicated children with ADHD compared to normal controls was found. This was not due to different levels of motor activity since correlation between activity and blink rate was low ($r = .04$, $p = .86$). This result is contradictory to Daughtery's finding (1993), however, it supports the results of the study by Caplan et al. (1996) who found a significant difference in eyeblinking between ADHD and control children in a verbal recall condition. Both studies reported no differences in the eyeblink rate between ADHD and control children during conversation or listening conditions. Caplan et al. (1996) concluded that ADHD is associated with a disturbed blink rate modulation rather than a decreased blink rate in general. This deficit in blink rate modulation might not be a function of dopamine but might reflect impaired modulation by the locus coeruleus and noradrenergic system, since schizophrenic children and adults (whose clinical conditions are associated with hyperdopaminergic states) have higher mean blink rates but do not differ in blink rate modulation (Karson, 1981; Caplan & Guthrie, 1994). The results of this study do not support this hypothesis since a significant group difference in eye blinking was found in a resting situation without any cognitive demands. Unfortunately, the design of the present study does not permit examination of eye blink variation within subjects and therefore conclusions about blink rate modulation cannot be made.

Children with TBI were found to suffer from a decreased eye blink rate compared to normal controls. This is in line with the study by Vreugdenhil et al. (1997) who also

reported higher ratings on ADHD symptom scales to be related to lower blink rates in children with AIDS. However, the underlying mechanism of decreased blinking in children with TBI still remains unclear. One possible explanation might be that the majority of the TBI children demonstrated structural cortical abnormalities on the MRT scans, with lesions in the frontal lobes being most common. Subsequent to lesions in the prefrontal cortex, an increase of subcortical dopamine levels has been demonstrated in rats (Pycock, Kerwin & Carter, 1980). The structural cortical abnormalities may have caused a down-regulation of the cortical inhibitory system resulting in a decreased spontaneous blink rate.

To summarize, the results of the present study demonstrate similar catecholamine changes in children with ADHD and children with TBI. Both groups showed chronic overactivation of the noradrenergic system and a less responsive EPI excretion after cognitive stress. The only difference between both clinical groups was a tonic overaction of the EPI system observed only in children with TBI. This seems clinically important, since low urinary EPI has been considered to be a good predictor for a robust behavioral response to stimulant medication whereas higher EPI might indicate the reverse (Pliszka et al., 1996). Thus, the benefit of stimulant medication in children with TBI has to be critically evaluated in further studies, until now there is at least one group study which has demonstrated efficacy of stimulants in 10 children with TBI (Hornyak, 1997).

Both clinical groups suffered from a decreased blink rate, which might reflect a hypofunctioning of the dopamine system. No group differences were observed in catecholamine functioning in ADHD children with and without a comorbid anxiety disorder or in TBI children with and without secondary ADHD. The latter point indicates that TBI necessarily seems to be followed by chronic catecholamine changes even in the absence of ADHD symptoms.

In the present study, no distinct biochemical correlates for inattentiveness or hyperactivity/impulsivity were found. In general, few significant correlations were observed among behavioral and cognitive measures and catecholamine changes. However, a moderately high negative correlation was found between the number of inattentive and hyperactive/impulsive symptoms and the EPI excretion post-stress as well as between between NE excretion pre-stress and an objective measure of activity. Taken together, these results indicate that higher severity of ADHD seem to be associated with larger biochemical changes.

Several limitations of the current study must be acknowledged. Although structured interviews were used for the diagnosis of mental disorders after TBI, the ADHD diagnosis

in our TBI group seems to lack validity as indicated by lower correlations between nurse and teacher report and actigraph data in the TBI group (r=-.3) (see also chapter 3). The current sample size is small, therefore these results require replication. However, this study adds further evidence that peripheral measures of catecholamines in response to specific, time-limited stressors are sensitive and may yield information about the role of the norepinephrinergic and epinephrinergic systems in pediatric behavioral disorders.

6. IS THE LOCATION OF BRAIN LESIONS ASSOCIATED WITH TBI PREDICTIVE OF THE DEVELOPMENT OF EITHER SECONDARY HYPER- OR HYPOACTIVITY?

6.1 INTRODUCTION

Until now, it remains unclear whether the same neural system that is believed to be affected in children with developmental ADHD is also affected by TBI in children who develop a secondary ADHD, although the location of lesions seen on magnetic resonance (MR) images in the setting of closed-head injury does overlap with the neuronal pathways implicated in developmental ADHD (Max et al., 1998; Zametkin et al., 1990; Sieg et al., 1995).

Herskovits et al. (1999) analyzed the spatial distribution of lesions in 76 children with closed head injury, 15 of whom had developed a secondary ADHD 3 months after the accident. After manual delineation of lesions, images were registered to the Talairach coordinate system. For each subject, registered images and secondary ADHD status were integrated into a brain-image database, which contains depiction (visualization) and statistical analysis software. Depiction of the data suggested that children who developed a secondary ADHD had more lesions in the right putamen than children who did not develop secondary ADHD; this impression was confirmed statistically. After Bonferroni correction, no significant differences were found between secondary ADHD status and lesion burdens for the right caudate nucleus or the right globus pallidus. However, the findings of this study have to be interpreted with caution, since children with pre-injury ADHD (19%) have not been excluded from analysis.

Although, loss of initiative and apathy syndromes are well known as common sequelae of many brain injuries, little research has focussed on the cause of hypoactivity in

pediatric patients. In a recent review, Joseph (1999) analyzed case reports that have included neuroimaging methods. He summarized that phenomena as apathy or major depression are more commonly associated with left lateral as well as bilateral frontal abnormalities, while disinhibitory states are more frequently observed with orbito-frontal dysfunction and frontal-striatal disturbances.

The study of brain-behavior relationships consists of several problems and major uncertainties on the exact delineation of brain structures involved in specific processes. These uncertainties are mainly due to the methods used in the study of brain-behavior-relationships which frequently rely on a group comparison design. Recently, Godefroy et al. (1998) examined several models and related statistical procedures for the study of brain-damaged patients and showed that the use of classification and regression trees (CART) (Breiman et al., 1984) provides the most appropriate analysis of brain-behavior relationships. The advantage of this procedure is that the extension of a lesion to multiple brain regions in each patients can be taken into account.

In classical brain damage studies, often imaging findings have been used for grouping patients according to lesion localization (e.g., left/right damage or frontal/posterior lesion) and the interpretation obeyed a subtractive logic, i.e., the poor performance of one group implies that the damaged region defining the group is required for task completion. This classical approach has proved its efficiency in delineating large cerebral regions associated with the neuropsychological outcome at the level of syndromes, such as aphasia, hemineglect, visual agnosia etc. (Heilman & Valenstein, 1985). However, the group comparison method has its limitation since lesion distribution obeys rules specific to the pathological process (e.g., vascular territory for stroke, etc.), and does not necessarily overlap with the functional organization of the brain. Besides, patients with traumatic brain injuries, as in the present project, normally suffer from multiple lesions in different brain regions (due to coup and contrecoup) which makes it impossible to subdivide them in distinct groups according to the location of lesion.

Therefore, the aim of this study was to determine whether there is an association between the location of lesions and the development of either secondary hypo- or hyperactivity in children with TBI by using the CART method.

6.2 METHODS

6.2.1 Data analyzed in the present study

Data of 37 children with TBI were analyzed. All children were right-handed. MRI scans from all TBI children were obtained and afterwards the location and volume of the lesion was documented by a neuroradiologist. The scans nearest to the date of assessment were used. Time between MRI scan and assessment varied between two weeks and three months. One child was excluded since time of MRI examination and assessment in this study was longer than 1,5 years. All of the remaining 36 children had a documented abnormality on their MRI scans. One has to take into account that the present analysis made use of the children's available MRT scans which were performed for clinical purpose. Therefore, MRIs varied with respect to pulse sequence, echo time, section thickness or field of view, etc.

6.2.2 Analysis of location of lesions

MRI scans were analyzed by a neuroradiologist who was blind to information about the subjects. Locations of lesions were documented based on a neuroanatomical coding systems described by Damasio and Damasio (1984). Rather than specify the kind of lesion, each abnormality including hematoma, contusion, infarct, or axonal-shear injury were generically designated as "1", whereas regions without any abnormality were coded with a "0". At a second step, lesions were combined in bigger clusters (e.g., pons, medulla, inferior olive, and pyramid to brainstem) in order to reduce the number of variables. 11 regions of interest (ROI) were chosen based on prior research on neuroanatomical correlates of ADHD and hypoactivity. The ROIs are listed in Table 6.1.

Table 6.1.
Regions of interest (ROI) entered in the classification and regression trees.

Frontal gyri: *including straight, orbital, superior, middle, inferior lesions*
Temporal gyri: *including superior, middle, inferior, insula, parahippocampal, fusiform lesions*
Parietal gyri: *including superior, angular, supramarginal lesions*
Occipital gyri: *including superior, middle, inferior, cuneus lesions*
Caudate: *including caudate head, caudate body lesions*
Putamen
Globus pallidus
Thalamus
Midbrain: *including superior/ inferior colliculus, periaquaeductal gray, red nucleus, substantia nigra lesions*
Brainstem: *including pons, medulla, inferior olive, pyramid, spinal cord lesions*
Cerebellum: *including vermis, cerebellar hemisphere, tonsils, dentate, horizontal fissure lesions*

6.2.3 Statistical analyses

The CART method is based on a binary decision tree to predict a nominal or ordinal dependent variable. The procedure is iterative and splits repeatedly data into smaller and smaller subsets so that the descendant groups are increasingly more homogenous with respect to outcome (secondary hyperactivity respectively secondary hypoactivity in this application). This is accomplished by considering all possible binary splits of the prognostic factor for each subset in the tree. The subset is subdivided by the split, which maximizes the distance between outcome rate in the two descendant groups. This recursive partitioning is continued along each branch until a minimum sample size for the subset is reached. Due to the small number of subjects, the partition criterion was set at five for the main splits and two for the subsplits.

6.3 RESULTS

Figure 6.1 shows the CART model for the development of secondary hyperactivity.

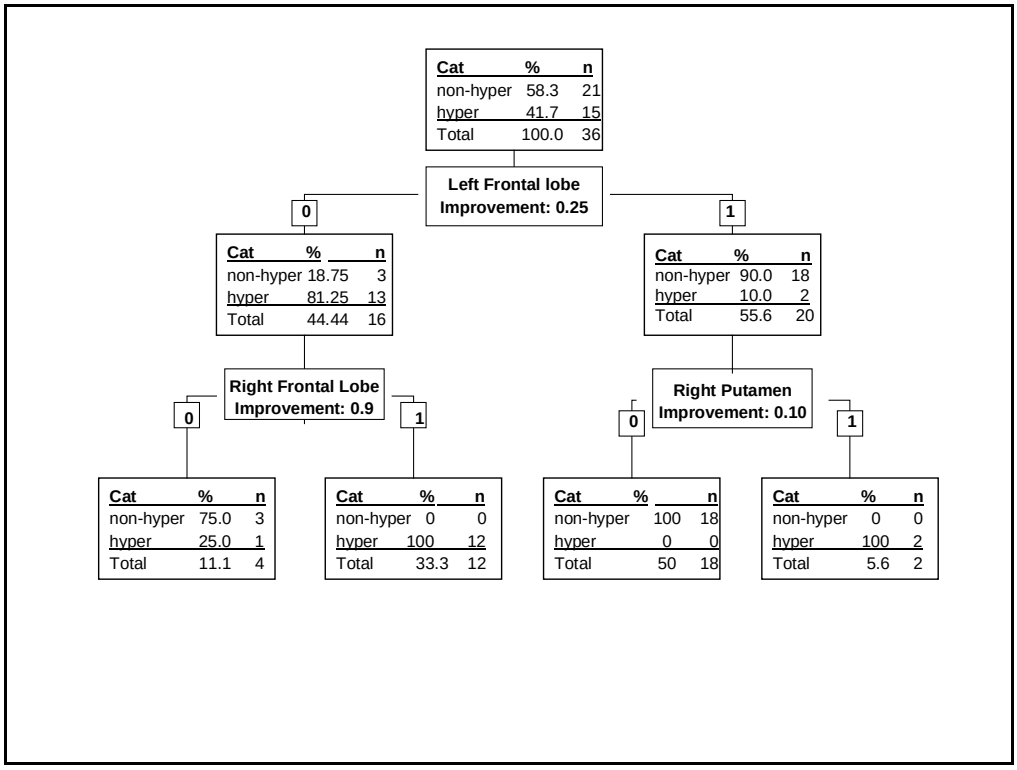

FIGURE 6.1. CART MODEL FOR THE DEVELOPMENT OF SECONDARY HYPERACTIVITY AFTER TBI. HYPER= SECONDARY HYPERACTIVITY; NON-HYPER= NO SECONDARY HYPERACTIVITY, 0= NO LESION; 1 = LESION.

As can be seen from Figure 6.1, hyperactivity was observed in the absence of left frontal lobe lesions (n= 13), but related to a right frontal lobe damage (n=12) or to an involvement of the right putamen (n=2).

In contrast, for the development of hypoactivity, brain stem lesions were highly predicitve (n=5). All four hypoactive children without brain stem involvement suffered from bifrontal lobe lesions.

Misclassification risks for the model were 2,8% for secondary hyperactivity and 0% for hypoactivity which means that localization of lesions were found to be highly predictive for any kind of activity disorders after TBI.

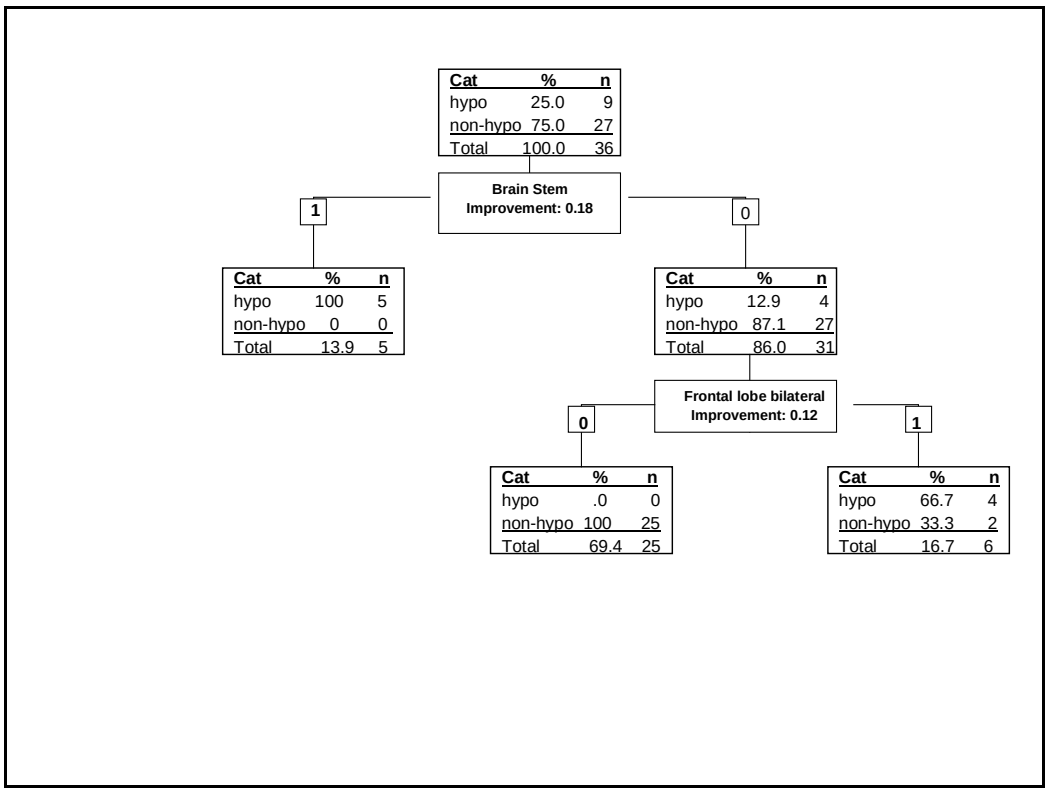

FIGURE 6.2. CART MODEL FOR THE DEVELOPMENT OF SECONDARY HYPOACTIVITY AFTER TBI. HYPO= SECONDARY HYPOACTIVITY; NON-HYPO= NO SECONDARY HYPOACTIVITY, 0= NO LESION; 1 = LESION.

6.4 DISCUSSION

The present analysis indicated that a close relationship between the location of lesions and the development of either secondary hyper- or hypoactivity can be observed in children with TBI. Since the classification and regression trees were not validated in a second independent sample, however, the interpretation of these data is only preliminary.

The results for postinjury hyperactivity are concordant with the neuronal pathways implicated in developmental ADHD (Tannock, 1998), indicating that both, developmental and secondary ADHD may be due to abnormalities in the right fronto-striatal networks. As in the study by Herskovits et al. (1999) a relationship between lesions in the right putamen and the development of secondary ADHD was found in children with TBI, whereas no association was detected between caudate nucleus or globus pallidus lesions and secondary hyperactivity. This finding is in contrast to the neuroimaging literature on developmental ADHD (Aylward et al., 1996; Castellanos et al., 1993; Singer et al., 1993). This difference may reflect underlying differences in the cause of developmental and secondary ADHD and may provide a starting point for investigation into the differences between these entities. Of interest, morphometric studies demonstrate loss of volume in the globus pallidus and the caudate nucleus (Aylward et al., 1996; Castellanos et al., 1993; Singer et al., 1993), but no lesions in children with developmental ADHD. Thus, ADHD may be a manifestation of any change in the basal ganglia.

An important confounding factor in the present analysis is the distribution of lesions in children with TBI, since, even if a neural structure were a critical component of the hypothesized ADHD pathway, it would be impossible to evaluate it if TBI only rarely caused lesions in this structure. For example, one possible reason for the detected association of right putamen lesions and secondary hyperactivity (but not globus pallidus lesions and secondary ADHD) is the relatively small number of lesions intersecting the globus pallidus (4 lesions versus 8 lesions for the right putamen). Therefore, the data have to be interpreted with caution.

Hypoactivity was more frequently observed in patients with lesions in the brain stem or in presence of bifrontal lobe lesions. This result can be moderated by severity of injury, since, generally, more severe traumata led more frequently to an involvement of brain stem lesions. Unfortunately, GCS scores were only available in 17 TBI subjects and were not measured in a standard manner (at admission, several days after the accident, not reported when they were administered, etc.). Therefore, correlation between GCS scores and brainstem involvement was low ($r = .2$), but this can also be due to the poor reliability of the GCS scores. However, this result is in line with Joseph's (1999) review of case reports that included neuroimaging methods and agrees with the general conclusion that phenomena such as apathy or hypoactivity are more commonly associated with bilateral frontal abnormalities, while disinhibitory states are more frequently observed with orbito-frontal dysfunction and fronto-striatal disturbances.

Taken together, the results of this study add further support that the application of the CART model is an appropriate method to examine brain-behavior relationships in patients with multiple lesions. Comparing neuroanatomical findings of children with mental disorders and brain-damaged children seem to be an interesting attempt to understand differences and similarities in brain mechanisms of organic and non-organic mental disorders.

7. GENERAL DISCUSSION

7.1 SUMMARY OF FINDINGS

Children with ADHD and children with TBI often present similar behavioral profiles, characterized by deficits in attention, organization and problem solving as well as fidgeting and poor affective control. When one searches for a shared underlying deficit present in both groups, the most obvious phenomenon seemed to be a deficit in the modulation and inhibition of inadequate responses.

Based on the empirical findings from ADHD research, an etiological model for ADH- symptomatology was presented which emphasizes that all three behavioral symptoms, inattention, hyperactivity and impulsivity might be associated with a cognitive or motivational deficit in inhibitory control which seems to be related to a functional hypofrontality which in turn, correlates with either structural or biochemical changes in the prefrontal lobes.

The present thesis encompasses four studies which addressed these etiological factors of ADH- symptomatology not only in children with developmental ADHD but extended the present research to the examination of children with TBI.

First, it was examined whether children with TBI and children with developmental ADHD suffer from a pervasive deficit in the inhibition of prepotent and ongoing responses, measured with the Stop-Signal and a Delayed-Response Task. The results indicate that both clinical groups have a similar deficit in their inhibitory control processes with respect to inhibition of both prepotent and on-going responses. Only children with TBI suffered additionally from a general slowing of their information processing which was not correlated with the inhibition deficit. A subdivision of TBI children according to actigraph data into hypo-, hyper-, and normokinetic subgroups revealed that the

hyperactive TBI children had inhibitory deficit patterns that were similar to children with developmental ADHD. It was concluded that slowing of information processing speed seems to be a general consequence of TBI in childhood, whereas slowing of the stop-processes or inhibitory deficits specifically, were associated with postinjury hypo- or hyperactivity.

Secondly, it was examined to what extent these inhibitory deficits can be influenced by motivational factors. Therefore, the Stop-Signal Task was performed with and without reward contingencies for successful inhibition. Results indicated that although all three groups showed a comparable learning effect in a retest condition, reward contingencies had different effects in the groups: whereas the performance of children with ADHD under reward contingencies was brought up to the level of performance in normal controls, rewards were found less effective in improving response inhibition in children with TBI. The results add support to a motivational explanation of the inhibitory deficit in children with developmental ADHD and provide evidence in favor of a non-motivational, primary response inhibition deficit due to structural brain damage in children with TBI.

The third study addressed the biochemical hypothesis whether there are differences in noradrenergic, adrenergic, and dopaminergic functioning in children with developmental ADHD, children with TBI and normal controls. For measurement the phasic and tonic activation of the norepinephrinergic and epinephrinergic system two urine samples were collected before and after a cognitive stressor. Spontaneous eyeblink rate was used as an indirect measure of central dopamine activity. The results suggest that children with TBI and children with ADHD, regardless of any comorbid diagnosis, excreted significantly more normetanephrine, the chief metabolite of NE, in the resting situations and less EPI after cognitive stress and showed a decreased blink rate compared to normal controls. Children with TBI also showed a higher excretion of metanephrine, the chief metabolite of EPI in the resting situation in comparison to children with ADHD and controls. Thus, both, children with ADHD and TBI may suffer from a higher tonic activity of the NE system and a less adaptive EPI excretion in response to mental stress, however, children with TBI seem to be additionally impaired in their tonic EPI excretion.

In the fourth study, the relationship between the location of lesions and the development of either secondary hyper-or hypoactivity was examined in children with TBI. CART models revealed that an involvement of the right frontal lobe or right putamen seemed to be an important risk factor for hyperactivity. This is in line with the study of Herskovits et al. (1999), who also found that TBI children who developed secondary

ADHD had more lesions in the right putamen than children who did not develop secondary ADHD. Neuroimaging studies in children with developmental ADHD suggest that the right frontal lobes and fronto-striatal networks may be involved in the etiology of ADHD (Tannock, 1998), indicating that both, developmental and postinjury ADHD, may have a similar underlying neuroanatomical correlate. For secondary hypoactivity, it was shown that brain stem involvement may put those children at higher risk for the development of hypoactive and abulic symptoms. These results are preliminary since the sample size was small and the CART models were not validated in a second sample. However, the misclassification risk was astonishingly low in both classification models (0% to 2.3%).

The findings of study 1, 2 and 3 suggest three differences for TBI children as compared to children with developmental ADHD: first, only children with TBI suffer from a deficit in response execution, indicated by longer go-reaction times in both inhibition tasks; second, only children with ADHD are able to achieve normal stopping performance under motivating conditions and third, only children with TBI show a tonic overactivation of the epinephrinergic system, measured by higher excretion of MN in the resting situation.

Hyperactive TBI children seem to be similar to children with developmental ADHD with respect to the following factors: Both show a dissociation between a relatively long SSRT and an unremarkable go-reaction time in the Stop-Signal Task and an inhibitory deficit of prepotent response inhibition in long delays. Biochemically, both groups show a tonic overactivation of the norepinephrinergic system. Besides, hyperactive TBI children also show fronto-striatal abnormalities as suggested before in neuroimaging studies with children with developmental ADHD (Tannock, 1998).

The similarities between TBI and ADHD children and the high prevalence of post-injury ADHD after TBI make the historical association of ADHD and brain damage (Barkley, 1990), as described in chapter 1.2.1, plausible. One could assume that due to selection biases especially children with any kind of brain pathologies were examined in earlier ADHD studies. However, despite the many similarities between brain injured children and children with developmental ADHD, the differences between both groups found in the present study make it necessary to carefully distinguish between primarily brain-damaged and non-brain-damaged children.

With respect to the etiological model of ADH symptomatology described in chapter 1.4, most aspects of this model, such as the inhibitory deficit, the influence of motivation at least for the developmental ADHD group and the biochemical changes in

the dopaminergic and norepinephrinergic systems were supported by the present experimental results. Thus, the model seems to represent a good framework for further research. However, several caveats are necessary: Most data are correlational in nature and the assumed direction of the relationship of the variables may be different from the one proposed. It is especially important to note that all patients were assessed after they had developed a primary or post-injury ADHD. It is well possible that the observed deficits are only a consequence rather than an antecedent. Prospective studies with children with behavioral inhibition deficits and children with an acute TBI are necessary to answer the pathogenetic relevance of the model.

7.2 IMPLICATIONS FOR THERAPEUTIC ISSUES

Although the present research lacks direct implications for the development of new treatment techniques in pediatric patients, study 2 and 3 offer some suggestions for behavioral and pharmacological treatment interventions.

Results of study two demonstrate the strong motivational impact on stopping behavior in children with developmental ADHD. Thus, reward contingency plans and token economies seem to be of special interest as treatment interventions in hyperactive children. In line with this, several meta-analyses indicate the efficacy of behavioral treatment programs for children with ADHD (Pelham & Hinshaw, 1992; Pelham et al., 1998) however, the longterm effects of such programs were found to be disappointing in follow-up studies (Pelham et al., 1998). The same effect was also observed in the longterm follow-up for stimulant medications, indicating positive effects only as long as the medication was continued (American Academy of Child and Adolescent Psychiatry [AACAP], 1997). No differences were found in the prognosis of treated and untreated children with ADHD (for a review, see AACAP, 1997). In the second study of this thesis, a positive *shortterm* effect of reward was found. This result differed from prior research, since Oosterlaan et al. (1998) found reward and response cost contingencies not effective in improving inhibitory deficits in children with ADHD. However, Oosterlaan did not make use of token economies. Thus, taken together, one could speculate, that children with ADHD need strong reinforcers (i.e. good tokens) and these reinforcers should be implemented into their environment for the whole life, if positive *longterm* effects should be achieved. This means that behavioral programs must offer possibilities for longlasting reward contingency plans which need to be regularly checked by a behavior therapist.

Further research will show whether such longterm reward plans are able to produce a better longterm outcome than the traditional behavioral programs.

The therapeutic consequences for children with TBI seem to be less promising. In the second experiment, a similar positive effect for reward contingencies was not found in the head injured group compared to the ADHD group, indicating that token economies might be less effective in improving behavioral disorders associated with impulsivity in children with TBI. Although therapeutic studies are rare in children with TBI, several studies indicate positive effects of behavioral treatment programs (Alderman & Ward, 1991; Slifer, Tucker & Gerson, 1996; Heubrock & Petermann, 1997). One has to take into account that these consisted mainly of case studies, and were not designed especially for TBI children with ADHD symptoms. For adults with TBI, the National Institute of Health (NIH) summarized in their recent consensus conference (1999) that studies investigating the effect of behavior modification programs for behavioral problems and personality change after TBI are mainly descriptive and provide only limited support for the efficacy of this approach. Another uninvestigated, but interesting, topic as far as behavior therapy is concerned remains the question of an effective treatment for the abulic or hypoactive symptomatology after childhood brain injuries. The present actigraph data suggest that hypoactivity is as frequent after TBI as secondary hyperactivity.

A second problem for therapeutic interventions in children with TBI could be the described overactivation of the EPI system, which is hypothesized as predictive for poor response to stimulant medication (Pliszka, 1996). Furthermore, children with TBI may be more likely to experience adverse effects from pharmacological agents than people without TBI (NIH, 1999). Therefore, strict indication criteria and additional caution in monitoring psychopharmacological side effects for stimulant medication in children with TBI are necessary.

7.3 METHODOLOGICAL ISSUES

Besides the methodological problems already mentioned above, there are several limitations in the present studies.

First, all hypotheses were tested on the same sample of children, which means, that further replication studies with independent samples are needed to crossvalidate the described findings. Second, the small N (26 to 37 per group) was at times problematic. Although it was sufficient for the analysis of group differences and change in the

experimental conditions, the sample size became critically low, when subgroups of patients, e.g., hyperactive or hypoactive TBI children were examined. Replication with larger numbers of subjects is warranted.

However, the sample analyzed in the present project seemed to be representative, since major characteristics, such as sex ratio and subtype distribution in the ADHD group (APA, 1994; Lahey & Carlson, 1992) or prevalence of secondary ADHD (Max et al., 1997) in the TBI group were concordant with prior findings. An advantage of the study, as far as external relevance is concerned, was that it included the majority of the representative population of ADHD and chronic TBI children. Only children with developmental delays, learning disabilities or chronic illnesses and in cases of TBI children with premorbid symptoms of ADHD were excluded. The results of this thesis can therefore be generalized to the majority of ADHD and TBI children. Further research will, however, have to examine subtypes of ADHD and subgroups of TBI children in order to determine differences in inhibitory control and biochemical changes as the results of the first and third study suggest.

Another major problem was the diagnostic process for pre- and post-injury ADHD symptomatology after TBI. First, the premorbid status of ADHD symptoms was only assessed by retrospective parent-based information, which may lack reliability. Therefore not all children with developmental ADHD may have been excluded. Second, the correlation between the actigraph data and the ADHD diagnosis based on teachers' and nurses' information was especially low for the TBI children. This may have been due to the fact that not the parents but the nurses of the rehabilitation center were interviewed. This information may have been less reliable, even though the nurses had more face-to-face-contact with the children over the previous three months. No use was made of a neuropsychiaric rating scale which differentiates between dysexecutive, abulic, and hypoactive or hyperactive symptoms. Thus, in further studies examining psychiatric consequences of TBI, neuropsychiatric rating scales or interviews, such as the Neuropsychiatric Rating Schedule (NRS) (Max et al., 1998), since the application of "normal" standardized diagnostic interviews for mental disorders in children and adolescents seems to be insufficient.

For the first and second experiment, limitations of the inhibition tasks should be acknowledged. Although the Stop Task has several advantages over other measures of response inhibition, the paradigm is restricted to the measurement of momentary motor inhibition, i.e., the ability to withhold a response over a short period of time and cannot be

generalized to the measurement of inhibition of complex cognitive processes (Osterlaan et al., 1998). Although, hyperactivity is more obviously associated with a deficit in motor inhibition, the inattentiveness and impulsivity as additional core symptoms of ADHD make the examination of inhibition of complex cognitive processes worthwhile. Furthermore, the Delayed-Response Task was discovered as non-optimal for measuring prepotent response inhibition under short-delay-conditions, since the reward (shortening of and avoidance of delay) for an impulsive reaction (firing immediately at the UFO) may have been too weak.

In the third study, another interesting point would have been to investigate blink rate modulation across different cognitive tasks (Caplan et al., 1996). Unfortunately, the present design did not take this into account.

In chapter 1.4 a simple model of the etiology of ADHD has been described. However, this model could not be tested as a whole, since the application of structural equation methods is restricted to bigger sample sizes. Tabachnick and Fidell (1996) recommend to make use of structural equation methods, if a sample size > 200 subjects is available.

7.4 IMPLICATIONS FOR FURTHER RESEARCH

The present thesis showed a number of similarities and differences between children with developmental ADHD and children with TBI. Thus, it seems to be useful to compare pediatric disorders with similar behavioral profiles in order to better understand underlying pathophysiological mechanisms. As described in chapter 1.3 the scope of the frontal methaphor is quite broad and provides analogies for several distinct behavioral pathologies. For example, in terms of developmental psychopathology, the pseudopathic syndromes provides a fairly close analogy for conduct disorder, akinetic mutism or the apathetic syndrome provides some similarities to autism, and the main analogy for Tourette Syndrome may be the deficit in inhibition observed after some frontal lesions (Pennington & Ozonoff, 1996). Thus, comparative research on primarily organic and primarily non-organic mental disorders in children may provide promising suggestions for the bio-psychosocial understanding of these disorders.

Although in the model presented in chapter 4 “functional hypofrontality” has been described as an important etiological factor in ADHD, it could not be examined in the present project. However, the CART model revealed that right frontal lesions put TBI

children at higher risk for developing secondary ADHD. In future research, neuroimaging methods, e.g. the functional MRI, should be applied to examine cognitive activation in the fronto-striatal network in children with developmental ADHD. However, there are several problems for the application of fMRI methods in hyperactive children, since for most of these children it is impossible to lie still during the procedure, and any sedative medication would bias the neuroimaging results. Additionally, PET and SPECT and studies may also reveal more specific information on the factor "hypofrontality" indicated by differences in regional cerebral blood flow or glucose metabolism. However, the application of these methods may be even more ethically problematic in children since subjects are exposed to low-dose radiation. Although these dosages are considered safe for healthy adults, children are more sensitive to radiation effects which makes it problematic to study physically healthy children, such as those with developmental disorders and normal control subjects (Krasuski, Horwitz & Rumsey, 1996).

Experiment two revealed motivation as a strong influencing factor on inhibitory performance in children with ADHD. However, the kind and degree of motivation were not manipulated. Further research should focus on a variation of motivating conditions (e.g., self-set or assigned goal setting, response cost versus partial or contingent reinforcement) in order to specify the motivational deficit in children with ADHD.

In the third study, differences in peripheral catecholamine excretion were found for ADHD and TBI children and normal controls. Therefore, it may be interesting to experimentally manipulate the peripheral catecholamines and examine the effects on behavior and performance. Another point of interest in this area may be psychopharmacological studies, as Solanto (1984) has already done them. For example, it may be interesting to investigate the cognitive performance on inhibition tasks during the intake of different doses of stimulants or noradrenergic agents. Especially for brain-injured patients there is a total lack of research in this field.

The fourth study showed that CART models are useful for the investigation of brain-behavior relationship. Unfortunately, we did not obtain the biochemical data of all 36 TBI children and therefore, it was impossible to calculate regression trees on the relationship between catecholamine changes and localization of lesions. However, this would be a very interesting point for further studies.

Provided that the results of this project are replicable and prove to be valid, they may have important consequences for the understanding of disorders of behavioral inhibition in childhood. With respect to the etiological model described in chapter 1.4 and

the findings of study 1 and 3, it can be suggested that results of further research may find clear biochemical or “inhibitory control” predictors which distinguish between children who develop a ADH- symptomatology and children who do not. Therefore, longitudinal research should follow up children with and without a disinhibitory symptomatology in early childhood as well as children with an acute TBI in order to assess the relationship between biochemical changes, inhibitory control deficits and the development of ADHD.

With respect to the TBI group, the findings of this thesis provide some hints that perhaps two distinct frameworks may be more appropriate for studying the consequences of TBI in childhood. Due to the described similarities between hyperactive TBI children and children with developmental ADHD, it seems to be possible to examine the development of secondary ADHD within the proposed model of ADH- symptomatology. However, the subgroup differences between hyper- and hypoactive children, as described in chapter 3 and 6, suggest that secondary hypoactivity may be associated with separate etiological factors which are described in a preliminary model in Figure 7.1.

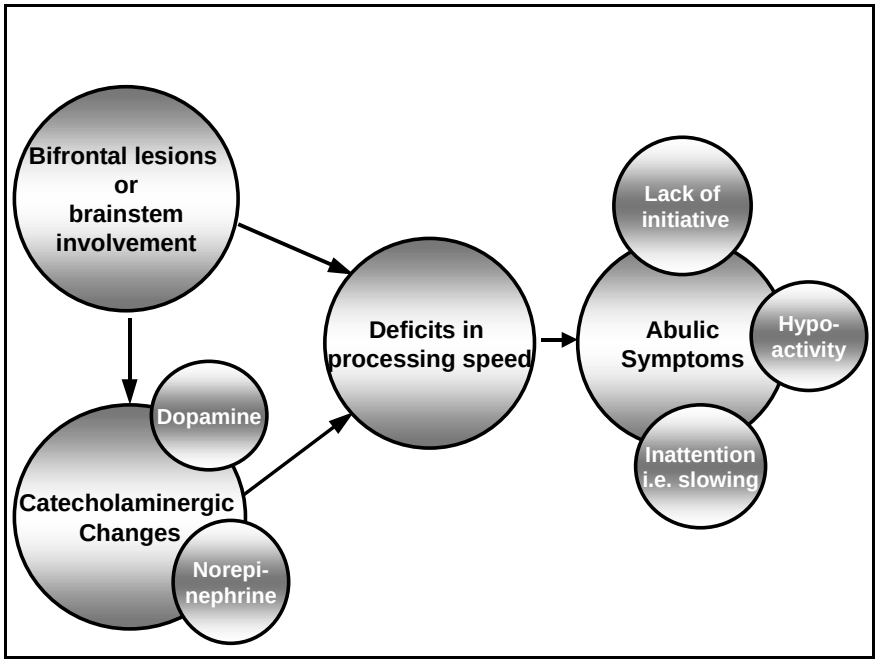

Figure 7.1. Proposed framework for the etiology of abulic symtpoms after TBI.

Due to the present results abulic symptoms seem to associated with a general slowing in information processing which may be related to bifrontal lesions or brainstem involvement which in turn may correlate with certain changes in the norepinephrinergic and dopaminergic systems.

The present thesis was a first attempt to clarify the relationship of biochemical, motivational, and inhibitory control factors in children with ADHD and children with TBI. At this point in time more questions are raised than can be answered. Subsequent research will have to evaluate the suggestions described in this thesis more carefully.

8. DEUTSCHE ZUSAMMENFASSUNG

Kinder mit einer Aufmerksamkeitsdefizit/ Hyperakvititätsstörung (ADHD) und Kinder nach einem Schädel-Hirn-Trauma (SHT) zeigen häufig ähnliche Verhaltensprofile, die durch motorische Unruhe, Aufmerksamkeitsstörungen, Impulsivität, Problemlösedefizite und eine geringere affektive Kontrolle gekennzeichnet sind (Arcia & Gualtieri, 1994; Benton, 1991; Donders, 1994). Das zu Grunde liegende Defizit dieser Verhaltensauffälligkeiten läßt sich am besten als eine Störung der Inhibition und Modulation von inadäquaten Reaktionen beschreiben (Pennington & Ozonoff, 1996; Anderson et al., 1998). Neben diesen funktionellen Ähnlichkeiten sprechen sowohl ADHD- als auch SHT-Kinder positiv auf eine psychopharmakologische Behandlung mit Stimulanzien, wie z.B. Methylphenidat und Dextro-Amphetamin, an (Hornyak et al., 1997; Solanto, 2000). Stimulanzien potenzieren den Umsatz von Dopamin und Noradrenalin im synaptischen Spalt, indem sie die Freisetzung der Katecholamine erhöhen, die Wiederaufnahme blockieren und in geringerem Umfang die katabolische Aktivität der Monoamino-Oxydase hemmen. Die vergleichbare Wirksamkeit von Psychostimulanzien bei ADHD- und SHT- Kindern kann als Hinweis darauf gewertet werden, daß bei beiden Gruppen ähnliche neurobiochemische Veränderungen in den zentralen Transmittersystemen zu Grunde liegen, insbesondere im Bereich des dopaminergen und noradrenergen Systems.

Auf der Grundlage der empirischen Befunde der ADHD- Forschung der letzten Jahre wurde ein ätiologisches Modell der ADH- Symptomatik abgeleitet, das davon ausgeht, daß alle drei Kardinalsymptome, die Unaufmerksamkeit, Hyperaktivität und Impulsivität auf ein zentrales Defizit in der Inhibition von Reaktionen zurückzuführen sind, welches wiederum bedingt ist durch eine funktionale Hypofrontalität, die ihr biochemisches Korrelat in Veränderungen zentraler Transmitterstoffe findet, insbesondere im Bereich des dopaminergen und noradrenergen Systems.

Entsprechend wurden in der vorliegenden Dissertation anhand von vier Fragestellungen kognitive, motivationale, biochemische und neuroanatomische Faktoren hinsichtlich der Ätiologie der Aufmerksamkeitsdefizit- und Hyperaktivitäts (ADH)-Symptomatik überprüft. Hierfür wurden insgesamt 94 Kinder untersucht, davon erfüllten 31 Kinder die DSM-IV-Kriterien für ADHD, 37 Kinder hatten ein SHT erlitten und 26 Kinder waren gesunde Kontrollkinder. Zu berücksichtigen ist, daß alle vier Teilstudien an

derselben Stichprobe durchgeführt wurden, d.h. eine Replikation der Ergebnisse an unabhängigen Stichproben ist unbedingt notwendig.

In der ersten Teilstudie wurde der Frage nachgegangen, ob hyperaktive Kinder und Kinder mit SHT ein pervasives Defizit in der Inhibition präpotenter und bereits initiierter Reaktionen im Vergleich zu gesunden Kontrollkindern aufweisen (Kapitel 3). Die Inhibitionsfähigkeit wurde mit Hilfe eines Stop-Signal- und eines Delayed-Response-Paradigmas untersucht. Die Ergebnisse bestätigten, daß beide klinische Gruppen ein Defizit in der Unterdrückung von präpotenten und bereits initiierten Reaktionen im Vergleich zu gesunden Kontrollkindern aufwiesen. Die SHT-Kinder zeigten darüber hinaus eine allgemeine Verlangsamung in den primären Reaktionszeiten, die nicht mit dem Inhibitionsdefizit korrelierte. Eine Subgruppenanalyse der SHT-Kinder, in der die Kinder mit Hilfe von Aktigraphdaten in hypo-, hyper- und normokinetische Kinder aufgeteilt wurden, ergab, daß die hyperaktiven SHT-Kinder eine ähnliche Dissoziation zwischen einer unauffälligen primären Reaktionszeit und einer Verlangsamung im Stop-Prozeß zeigten wie die Kinder mit einer hyperaktiven Entwicklungsstörung. Hypoaktive SHT-Kinder wiesen hingegen sowohl längere primäre Reaktionszeiten als auch längere Stop-Signalreaktionen als normokinetische SHT-Kinder auf. Dies deutet darauf hin, daß eine primäre Verlangsamung der Informationsverarbeitungsgeschwindigkeit eine häufige, unspezifische Folge des SHTs darstellt, wohingegen eine Verlangsamung der inhibitorischen Prozesse mit der posttraumatischen Entwicklung einer Hyper- oder Hypoaktivitätsstörung assoziiert zu sein scheint.

In der zweiten Teilstudie wurde der Frage nachgegangen, inwieweit diese Inhibitionsdefizite durch motivationale Faktoren beeinflußt werden können (Kapitel 4). Da vorangegangene Studien bei ADHD- Kindern darauf hingewiesen haben, daß es sich bei der Inhibitionsstörung möglicherweise nicht um ein kognitives, sondern um ein motivationales Defizit handelt (Sanders, 1983; Sonuga-Barke, 1995; Barkley, 1997), wurde angenommen, daß hyperaktive Kinder sich in der Stop-Signal Aufgabe in einer Bedingung mit kontingent positiver Verstärkung bei erfolgreicher Inhibition nicht von gesunden Kontrollkindern in ihren Stop-Signal-Reaktionszeiten unterscheiden, während SHT-Kinder auf Grund ihrer strukturellen Hirnschädigung auch unter motivationssteigernden Bedingungen eine Beeinträchtigung in der Inhibitionsfähigkeit aufweisen. Die Ergebnisse bestätigten, daß, obwohl alle drei Gruppen in einer Wiederholungsbedingung den gleichen Lerneffekt zeigten, nur die inhibitorische Leistung der ADHD-Kinder in der Belohnungsbedingung sich nicht von der Leistung gesunder Kontrollkinder unterschied.

Die Effektstärke für den Einfluß der Motivation auf den Stop-Prozeß in der Gruppe der ADHD-Kinder war in der Größenordnung vergleichbar mit dem in der Studie von Tannock (1989) berichteten Effekt von Methylphenidat auf die Inhibitionsleistung hyperaktiver Kinder. Dieser Befund stimmt überein mit den Ergebnissen der Therapieforschung, die gezeigt haben, daß sowohl die Anwendung verhaltenstherapeutischer „Token- Economy“ -Systeme als auch die Psychostimulanzienbehandlung bei ADHD eine vergleichbare Wirksamkeit zeigt (Pelham et al., 1998). Die Ergebnisse des Experiments sprechen für eine motivationale Erklärung der Inhibitionsstörung bei Kindern mit einer hyperaktiven Entwicklungsstörung, wohingegen es sich bei SHT-Kindern um ein durch die Hirnschädigung bedingtes, primäres, nicht-motivationales Defizit zu handeln scheint.

In der dritten Fragestellung wurde die „Katecholaminhypothese“ hinsichtlich der Ätiologie von ADH- Symptomen untersucht (Kapitel 5). Zur Messung der phasischen und tonischen Aktivität des noradrenergen und adrenergen Systems wurden jeweils eine Urinprobe vor und nach einem kognitiven Stressor gewonnen und die Ausschüttung der Katecholamine und ihrer Hauptmetaboliten analysiert. Als indirektes Maß für die zentrale Dopaminaktivität wurde die spontane Blinzelfrequenz gemessen. Die Ergebnisse zeigten, daß Kinder mit ADHD und Kinder mit SHT, unabhängig von komorbiden Diagnosen, signifikant mehr Normetanephrin, dem Hauptmetaboliten von Noradrenalin, in der Ruhesituation ausschütteten als gesunde Kontrollkinder. Ferner zeigten sie eine geringere Zunahme der Adrenalinauschüttung nach dem kognitiven Stressor als die Kontrollkinder. Bei beiden klinischen Gruppen scheint eine tonische Überaktivierung des noradrenergen Systems vorzuliegen verbunden mit einer geringeren Adaptationsfähgikeit des adrenergen Systems, auf externe Anforderungen mit einer gesteigerten Ausschüttung von Adrenalin zu reagieren. Die SHT-Kinder wiesen darüber hinaus eine tonisch erhöhte Aktivierung des adrenergen Systems auf, die sich in einer signifikant erhöhten Ausschüttung von Metanephrin, dem Hauptmetaboliten von Adrenalin, in der Ruhesituation zeigte. Sowohl die SHT-Kinder als auch die ADHD-Kinder zeigten ferner eine signifikant niedrigere spontane Blinzelfrequenz. Dies unterstützt die Hypothese einer dopaminergen Unteraktivierung in der Ätiologie von ADH- Symptomen.

Die Anwendung bildgebender Verfahren bei Kindern mit einer hyperaktiven Entwicklungsstörung haben Hinweise auf eine Beteiligung rechts frontaler (Casey et al., 1997) und fronto-striataler (Castellanos, 1996) Strukturen hinsichtlich der Ätiologie von ADH- Symptomen gegeben. In der vierten Teilstudie wurde deshalb der Zusammenhang

zwischen der Entwicklung einer posttraumatischen Hyper- oder Hypoaktivitätsstörung und der Lokalisation der Läsion bei Kindern mit SHT untersucht (Kapitel 6). Da auf Grund der multiplen Läsionsorte bei SHT-Kindern keine Subgruppenbildung nach dem Schädigungsort möglich ist (Godefroy et al., 1998), wurde die Analyse mit Hilfe eines Classification- und Regression Tree- (CART)- Modells durchgeführt (Breimann, 1984). Anhand von 11 “regions of interest” wurde versucht, die Entwicklung einer Hyper- oder Hypoaktivitätsstörung vorherzusagen. Die CART- Modelle zeigten, daß eine Beteiligung rechts frontaler Strukturen oder des rechten Putamens bedeutsame Risikofaktoren für die Entwicklung einer sekundären Hyperaktivitätsstörung nach SHT darstellen. Dies steht in Übereinstimmung mit den Ergebnissen bildgebender Studien bei der hyperaktiven Entwicklungsstörung (s.o.) und spricht dafür, daß ähnliche Strukturen an der Entwicklung einer sekundären Hyperaktivitätsstörung wie bei der hyperaktiven Entwicklungsstörung beteiligt sind. Hypoaktivität wurde hingegen nur bei Kindern mit einer Hirnstammbeteiligung oder bei bifrontalen Läsionen beobachtet. Eine Konfundierung mit dem Schweregrad des Traumas konnte in der vorliegenden Analyse nicht ausgeschlossen werden. Das Ergebnis stimmt jedoch mit den Befunden einer Metaanalyse von Kasuistiken bei hirngeschädigten Patienten überein, die ebenfalls für einen Zusammenhang von bifrontalen Läsionen und Apathiesyndromen spricht (Joseph, 1999). Die Fehlklassifkationsraten der CART-Modelle lagen zwischen 0 und 2.3%, d.h. der Lokalisation der Läsion kommt eine hohe Bedeutung bei der Entwicklung posttraumatischer Aktivitätsstörungen zu.

Die Ergebnisse der vorliegenden Arbeit unterstützen die Annahme, daß inhibitorische Defizite und biochemische Veränderungen in der Aktivität des adrenergen, noradrenergen und dopaminergen Systems wichtige Faktoren hinsichtlich der Ätiologie einer ADH- Symptomatik darstellen und somit das in Kapitel 1.4 vorgestellte Modell eine gute Grundlage für weitergehende Forschung bietet. Allerdings bleibt dabei unbedingt zu berücksichtigen, daß die meisten Daten dieser Studie korrelativer Natur sind und Kinder untersucht wurden, die bereits die Kriterien für eine ADHD erfüllen, so daß es genauso auch denkbar ist, daß die beobachteten Inhibitionsdefizite und biochemischen Veränderungen eine Folge und nicht ein Antecedens der ADH- Symptomatik darstellen. Prospektive Studien sind deshalb notwendig, um die pathogenetische Relevanz des Modells zu überprüfen.

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