REM SLEEP AND AGGRESSIVE BEHAVIOUR IN CHILDREN WITH TOURETTE'S SYNDROME (TS), ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) AND COMORBID TS AND ADHD

by

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A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy
Department of Human and Applied Psychology
Ontario Institute for Studies in Education of the University of Toronto

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Abstract

Introduction: Many children with Tourette's Syndrome (TS) present clinically with aggressive behaviour and sleep difficulties. Behavioural difficulties are often more problematic than tics, and can disrupt school progress, family relationships and social development.

Objective: This study examined the relationship between polysomnographic sleep parameters, serotonin (5HT), testosterone (T), Executive Functioning (EF) and aggressive behavior at home and school in children/adolescents.

Method: 80 subjects (57 male / 23 female), were assessed using a semi-structured clinical interview (20 TS, 20 TS + ADHD, 20 ADHD and 20 Controls). All were medication free and between 6-16 years of age (mean 10.31 years, SD 2.35). Subjects participated in a 2-night sleep study and neuropsychological testing. The primary sleep variables were REM sleep latency and percentage REM sleep. Urine and saliva samples were used to measure 5HT and T levels. Pubertal maturity was assessed and parents and teachers completed behavioural questionnaires.

Results: Analysis of Covariance (ANCOVA), revealed significant group differences in % REM and REM latency variables (p<.018 and p<.004), T (p<.006), and ratings of aggressive behaviour (p<.020 and p<.006 respectively). Both the TS only and ADHD groups showed increases in REM sleep latency (p<.029) and reductions in percent REM sleep vs. Controls (p<.037). Ratings of aggressive behaviour in the TS+ADHD and ADHD groups were significantly higher than Controls. No significant differences were found on measures of EF.

Discussion: Differences among groups of children with TS, ADHD, TS+ADHD, and Controls were found in REM activity, ratings of aggressive behaviour, and T levels. Children with TS were significantly more aggressive than Controls when also comorbid for ADHD, supporting heterogeneity within the population of children with TS, and the importance of considering comorbid psychiatric diagnoses. A linear combination of physiological and cognitive variables accounted for a significant amount of variance in parental ratings of aggressive behaviour after diagnostic classification had been accounted for in the regression model, consistent with a 'spectrum' notion of psychopathology in which differences among diagnostic groups are better explained by including variables that may serve as putative markers of underlying pathophysiological processes.
Acknowledgments

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“Do not go where the path may lead, go instead where there is no path and leave a trail.”
Ralph Waldo Emerson (1803-1882)
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Developmental psychopathology of Tourette’s Syndrome

Tourette’s Syndrome (TS) is a lifelong, inherited neurodevelopmental disorder usually present in childhood, characterized by unwanted, repetitive, recurring involuntary motor and vocal tics, which present in a waxing and waning pattern. Onset of TS can occur as early as one year of age, with a mean onset age of 7.4 years, but always before age 18 (American Psychiatric Association, 1987; Wand, Matzow, Shady, Furer, & Staley, 1993; Shady, Fulton, & Champion, 1988). Similar to most neurodevelopmental conditions, TS is more common in males than in females, with a sex ratio of 3:1 reported in most epidemiological studies e.g. (Robertson, 1989). Conceptually, the TS phenotype is viewed as a product of a heightened, but selective sensitivity to changes in both the internal state of the body (similar to a somatic hyperawareness), and the external psychosocial environment. Descriptively, the range of symptoms in TS is enormous, and includes both motor and phonic tics (sudden repetitive movements, gestures, or utterances), that typically mimic some aspect of normal behaviour, and obsessions and compulsions (sudden repetitive thoughts, images urges and actions which are intrusive and difficult to resist) (Leckman & Cohen, 1999). A significant number of individuals within the clinical population of TS also suffer from attentional difficulties, impulsivity, and disruptive behaviours that often overshadow the tic symptoms as a source of impairment for both the child and their family (Nolan, Sverd, Gadow, Sprafkin, & Ezor, 1996).

Historical Development

In 1885 a young Charcot-trained neurologist at the Salpetriere Hospital in Paris France named Georges Gilles de la Tourette (Cohen & Leckman, 1999) originally described the symptoms of nine patients with complex tics which he considered a genetic disorder. Tourette
initiated the original neurological investigations on the organization and nature of this tic disorder, which now bears his name. In his original manuscript, Tourette made no reference to anatomical or pathological cause and referred scientists who were interested in pursuing pathophysiological mechanism to the field of psychology (Singer, 1997). Although once described as a rare condition, most recent prevalence estimates of TS are 1% of the general population (Kadesjo & Gillberg, 2000) (Mason, Banerjee, Eapen, Zeitlin, & Robertson, 1998). This relatively common hereditary tic disorder may have autosomal dominant mode of inheritance, however there is increasing support for a mixed model (Walkup et al., 1996; Barr & Sandor, 1998; Rutter, Silberg, O'Connor, & Simonoff, 1999), i.e. inherited genotype with partial penetrance and interactions with psychological factors.

Over the years the variations of TS expression have interested neurologists, geneticists, psychiatrists and neuroscientists as they investigated the boundaries between voluntary and involuntary tics and the links between neural substrates and complex and perplexing mental and behavioural phenomena (Singer, 1997). Since the first paper by Gilles de la Tourette (Gilles de la Tourette, 1882), TS has been described in terms of a variety of paradigms that have reflected the emergence of new conceptual schemas. Until the end of the nineteenth century TS was studied in the context of hysteries and choreas or choreiform disorders (Freud, 1953), then, with the upsurge of interest into psychoanalytical theories in the 1940s, the understanding of TS was framed within the perspective of psychoanalytic theories of character, obsessive compulsive neurosis and narcissism (Cohen & Leckman, 1994). In 1961, following the discovery of the efficacy of haloperidol in reducing tics in TS (Seignot, 1961; Kushner, 1999), the disorder was described as a neurochemical dysregulation. Earlier theories were then replaced by proposals involving specific brain pathways and biochemical abnormalities. Modern research encompasses a wide range of theoretical and clinical foci which include; defining the underlying genetic vulnerability (Barr et al., 1999; Pauls & Leckman, 1986; Leckman et al., 1997; Pauls, Raymond,
Stevenson, & Leckman, 1991), exploring the complex psychological phenomena, such as the
influences of the family and personal experience of the child (Wand et al., 1993), and comorbid
neurobehavioral disturbances (hyperactivity, self-injurious behaviour, obsessive compulsive
behaviour, rage, learning disabilities) (Sandyk, 1995). These combined points of view have
evolved over the past half century, with TS being conceptualized as a neurological disorder with
psychological consequences when seen by neurologists, or a psychiatric disorder with a
biological basis when seen by psychiatrists (Cohen et al., 1999).

Children with TS rarely present with tics alone, as they tend to be accompanied by other
cognitive and behavioural difficulties. The most common comorbid disorders are Attention
Deficit Hyperactivity Disorder (ADHD) (Towbin & Riddle, 1993) and Obsessive Compulsive
Disorder (OCD) (Leonard et al., 1992) along with anger control problems, sleep difficulties,
learning disabilities and emotional problems (Walkup, Scahill, & Riddle, 1995; Scahill, Leckman,
& Marek, 1995; Stephens & Sandor, 1999; Sandor, 1993). These common comorbid conditions
or disturbances tend to complicate the interpretation of behavioural and executive function
studies since, by definition, those domains are both partially overlapping and interrelated.

Comorbid Disorders

It was suggested by Comings et al. (Comings & Comings, 1988) through their
observation that increased tic severity were concurrent with increased severity of ADHD, that
the two disorders somehow shared a common neuronal substrate. To date, ADHD and TS have
not yet been explained by any inheritance models (Pauls, Towbin, Leckman, Zahner, & Cohen,
1986) or entirely to sampling biases (Fallon & Schwab-Stone, 1992), which suggests that there
are factors in addition to genetics or ascertainment biases contributing to the comorbidity of TS
and ADHD. Most recently, epidemiological studies suggest the presence of a diagnosis of TS
increases the risk, or vulnerability for developing an additional disorder, e.g. ADHD (Zohar et
Sheppard et al. (Sheppard, Bradshaw, Purcell, & Pantelis, 1999) reported that although it is clear that children with TS are somewhat predisposed to develop ADHD, children with ADHD do not seem to demonstrate a greater risk than normal of developing TS. There is strong support from segregation analyses studies for a genetic relationship between TS and OCD (Pauls, 1992) while on the other hand, no support for a genetic association between ADHD and TS has been found.

**Attention Deficit Hyperactivity Disorder**

According to epidemiological studies, Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common chronic disorders of childhood, with prevalence estimates varying from 1-7% in the general population, depending on the diagnostic criteria applied (Hinshaw, 1994). Sex ratios for example, in epidemiological studies suggest a male: female ratio of 3:1 (Szatmari, 1992). Primary symptoms of ADHD are hyperactivity, impulsivity and distractibility. Diagnostic criteria require that symptoms must be observed in two or more settings by a combination of teachers, parents and health care professionals and recorded by means of standardized questionnaires. ADHD is often associated with reading disability (RD) (Shaywitz et al., 1994), conduct disorder (CD) (Moffitt, 1993) (Biederman, Newcorn, & Sprich, 1991) depression (Biederman et al., 1993) Tourette's Syndrome (TS) (Sverd, Curley, Jandorf, & Volkersz, 1988; Spencer et al., 1998) and other disorders. More than half of the children diagnosed with ADHD meet criteria for a comorbid diagnosis (Milberger et al., 1995) (Kadesjo & Gillberg, 2000).

In children with TS, ADHD symptoms frequently present before the onset of tics, and are present in about 50-70% of the clinical population (Schuerholz, Baumgardner, Singer, Reiss, & Denckla, 1996; Spencer et al., 1998; Bruun & Budman, 1992).
Obsessive Compulsive Disorder

Obsessive compulsive symptoms have been observed in patients with TS since Gilles de la Tourette's own reports of patients (Gilles de la Tourette, 1882). Obsessive Compulsive Disorder (OCD) is considered a chronic, disabling mental condition where patients repeatedly experience the sudden intrusion into consciousness of unwanted worries or unpleasant images and repeated urges to perform seemingly senseless acts (Leckman et al., 1997). The association between TS and OCD was first documented in family studies (Pauls et al., 1986) when an elevation of OCD in first-degree relatives of TS probands was reported. Epidemiological studies suggest that 42% to 49% of TS patients also suffer with significant obsessive compulsive symptoms (Price, Pauls, Kruger, & Caine, 1988; Apter et al., 1993; Tanner & Goldman, 1997). Recently reported study of relatives of 100 probands with obsessive-compulsive disorder, found that 4.6% of the relatives had tics or TS (Pauls, Alsobrook, Goodman, Rasmussen, & Leckman, 1995). The effectiveness of serotonergic reuptake inhibitors in treating OCD symptoms (Goodman, McDougle, & Price, 1992; McDougle et al., 1993) in addition to emerging evidence for serotonergic alterations in OCD (Rauch et al., 1997), suggests that dysfunction of the serotonergic system is of central importance in neuropathology of OCD and perhaps also TS (Anderson, Leckman, & Cohen, 1999).

Results from an international survey of 3500 TS patients (Freeman, 2000) found the percentage of anger control problems in individuals with TS only, fell at 10%, similar to that reported in the general population (Caron and Rutter, 1991: Costello et al, 1996; Budman et al, 1998; Stephens and Sandor 1999) however the prevalence increased to 16% in those with TS and comorbid OCD (Freeman, 2000). Interestingly, when the triple comorbid group of patients with TS + ADHD + OCD were examined, the incidence of aggressive behaviour increased
dramatically to a highly significant 40%. Also, in this group with three diagnoses there were almost twice as many sleep problems (27%) and four (4) times as many social problems (13%) than the TS only patients (14% and 3% respectively). The marked increase of anger control and sleep problems observed in the comorbid TS group compared to the patients with TS only, was consistent with previous studies which have observed that the risk of anger control problems in the TS population increases with the additional diagnoses of ADHD and OCD (Allen, 1992; Budman, 1998; Halperin, 1997; Kruesi, 1990; Linnoila, 1983). It has been suggested by these studies that a disturbance in the central serotonergic functioning understood to be associated with OCD and ADHD may be compromising the frustration tolerance in children with TS, resulting in increased aggressive responses.

Although studying the sleep of children with TS + OCD and pure OCD is of great interest, these diagnostic groups were not included in this phase of the study because of time and resources constraints.

**Aggression and Rage Attacks**

The association between TS and disruptive behaviour problems and aggressive behaviour was described in 1974 by Moldofsky et al (Moldofsky, Tullis, & Lamon, 1974). Two thirds of their clinical sample exhibited aggressive behaviour. Stefl (Stefl, 1984), found that 65-75% of individuals with TS reported behavior problems, including temper outbursts, hyperactivity, mood swings, and aggression. According to Comings (Comings & Comings, 1985), the best descriptor of a behavioral problem in children with Tourette's is “anger”. They reported 42% of their TS sample (N=250) having problems with both anger and violence, with the severity outside the normal range already surpassed by the grade one level. When considering the group with hyperactivity and TS, by grade two, 59% of the children were experiencing severe aggression problems. These findings applied to both the male and female subjects. Recent
clinical observations in the Tourette's Clinic at Toronto Western Hospital, show that 31% of the referred TS population is experiencing problems with rage and aggressive behaviours. This is in agreement with reports from other similar clinics worldwide (Freeman et al., 2000). Characteristics of the aggression and rage found in the TS population include: 1) anger outbursts out of proportion to the precipitating event, 2) general irritability and low frustration levels, 3) inability to take "no" for an answer, 4) rage and verbal abuse usually aimed at their mother, and 5) anger often followed by remorse. A study of clinically referred TS children found rates of aggression to be particularly elevated in those who also have comorbid ADHD and/or Obsessive Compulsive Disorder (Budman, Bruun, Park, & Olson, 1998; Stephens et al., 1999).

In contrast, Park et al. (1996) reported in a study of 55 children with TS, that neither the single addition of ADHD nor OCD to TS predicted the occurrence of rage attacks. They found that comorbidity of all three disorders, TS, OCD and ADHD, was highly correlated with the presence of rage attacks. These results cannot be generalized because all of the above papers were describing selected clinical populations from highly specialized clinics.

**Sleep disturbances**

"Sleep is the primary activity of the developing brain in childhood" (Dahl, 1998). Although there is no clear model of why sleep is important or what specific function is served during the large proportion of time children spend asleep, there have been numerous associations observed between the amount and quality of sleep and the regulation of attention and arousal (Trommer, Hoepner, & Rosenberg, 1988; Kaplan, McNicol, & Conte, 1987), affect (Dahl, 1999) and social behaviour during wakefulness (Dahl, 1998). An elevated frequency of sleep problems has been reported in children and adolescents with attention-deficit hyperactivity disorder (Corkum, Moldofsky, Hogg-Johnson, Humphries, & Tannock, 1999; Kaplan et al., 1987; Pat-Horenczyk, Stein, Barak, Ring, & Epstein, 1997; Giannotti, Cortesi, & Ottaviano,
1997), and other behavioral problems of clinical significance (Simonds, 1984; Morrison, McGee, & Stanton, 1992). It is estimated that 25-60% of the clinical population of TS also complains about disturbed sleep (Freeman et al., 2000), and, although the specific neural or physiologic functions served by attaining “adequate” sleep are still unknown, it is understood that sleep is as important for maintaining life as food or water (Dahl, 1999). Additional research supporting a “bidirectional relationship between inadequate sleep and dysregulation of daytime behaviour includes: emotional distress or sudden behavioural disturbances interfering with sleep onset, or related to sleep loss (Dahl, 1996), an overlap in the neurobehavioural systems involved in both sleep/arousal and in behaviour and affect regulation (Dahl, 1998) and studies indicating the predictability of later childhood behavioural and emotional problems from early and persistent sleep problems (Dahl, 1999).

**REM Sleep and Behaviour**

Rapid eye movement (REM) sleep, known as “paradoxical sleep”, “desynchronised sleep” or “dream sleep” (Gulyani, Majumdar, & Mallick, 2000), is probably required for proper development and maturation of the central nervous system (CNS) according to the “Ontogenic hypothesis” (Roffwarg, Muzio, & Dement, 1966). While the synthesis and turnover of proteins in the brain has been thought to be proportional to brain maturation, it has been hypothesized by Stern & Morgane (1974) that “REM sleep probably maintains the functioning of the aminergic system and protein synthesis in the central nervous system”. The well-documented natural decline of percent of REM sleep with age is thought to reflect CNS maturation (Coble, Kupfer, & Reynolds, 1987). Interestingly, Ramos Platon et al. (1990) reported the inverse (REM percentage increasing with age) in a polysomnographic study of children affected with Attention Deficit Disorder (ADD). This may indicate a possible CNS maturational abnormality (Ramos Platon et al., 1990). Prolonged REM latency was also noted in children with ADD with
hyperactivity (ADD/H) compared to ADD without hyperactivity (ADD/WO), revealing a similarity between children with ADD/H and depression.

REM sleep has been associated with localized changes in brain metabolism (Lydic et al., 1991) and increased brain blood flow (Reivich, Isaacs, Evarts, & Kety, 1968; Shapiro & Rosendorf, 1975) (Meyer, Ishikawa, Hata, & Karacan, 1987) while REM sleep deprivation has been shown to produce a generalized increase in neural excitability (Gulyani et al., 2000). Notably, since the deprivation induced effects reversed after REM sleep recovery, it is plausible to assume that at least one of the functions of REM sleep could be the maintenance of the neuronal excitability status (Gulyani et al., 2000). REM sleep deprivation has also been associated with several instinctive and motivational behaviours, e.g. fighting (Morden, Conner, Mitchell, Dement, & Levine, 1968) and hypersexuality, thus affecting the modulating effects of testosterone on male sexual behaviour in rats (Velazquez-Moctezuma, Salazar, & Retana-Marquez, 1996). It has also been observed that REM sleep deprivation renders serotonergic dorsal raphe neurons less sensitive to the inhibitory effect of serotonin reuptake blockers, thus altering acquired behaviours (Gulyani et al., 2000). Collectively, these findings have led to the hypothesis that REM sleep plays an important role in maintaining normal physiology and behaviour.

Sleep problems and Cognitive Functioning

Recently, Dahl (Dahl, 1999) described a model of the relationship between sleep deprivation and prefrontal cortex functioning. He suggested that although children may not appear outwardly sleepy, they may manifest behavioural problems such as impulsivity, distractibility, emotional lability and “disinhibition” due to inadequate or disrupted night time sleep. In fact, although these children were sleeping for an appropriate length of time, their overall quality of sleep was very poor, and subsequently their daytime behaviour was impaired. The relationship between sleep quality and cognitive functioning in children has scarcely been
investigated and as a result there is a lack of controlled studies in this area and a dearth of data on the possible long term effect of insufficient sleep, both quantitatively and qualitatively, on children's cognitive and behavioural functioning and development.

**Sleep problems in TS**

*Subjective Reports*

An early report of frequent "sleep disturbance" was noted in 22 of 50 patients with TS (Nee, Caine, Polinsky, Eldridge, & Ebert, 1980). Subsequently sleep difficulties have been reported regularly based on the subjective experience of the patients or observations of their family members. Moldofsky et al. (Moldofsky et al., 1974) found that 12 of 15 TS patients suffered from initial insomnia, and/or frequent awakenings, while Barabas et al. (1984) reported for the first time an increased incidence of parasomnias in a sample of 50 boys and 70 girls aged 5 to 21 years. They noted that 17.5% of the patients with TS reported somnambulism, 15.8% suffered from night terrors and 18.9% experienced enuresis after the age of seven years, rates exceeding those of comparison groups, i.e. children with seizures and learning disabilities. The incidence of at least one of the above sleep disorders was 38.6% for the children with TS, compared to 10.3% for the group with seizures and 17% for children with learning disabilities.

Jankovic et al. surveyed the sleep patterns of 112 TS patients and found 62% suffer from some form of sleep disturbance (Jankovic, Glaze, & Frost, 1984), with 19% identifying enuresis, and 12% reporting insomnia and restless sleep as the number one problem (Trajanovic, Shapiro, & Sandor, 1997).

*Objective (Polysomnographic) Studies*

A very limited number of polysomnographic sleep studies have been conducted in TS patients with conflicting results (See Table 1).
<table>
<thead>
<tr>
<th>Study</th>
<th>Sleep Efficiency</th>
<th>Sleep Latency</th>
<th>Amount of Slow Wave Sleep</th>
<th>Amount of REM Sleep</th>
<th>Total Sleep Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Mendelson, Caine, Goyer, &amp; et al, 1980)</td>
<td>Unaffected</td>
<td>Unaffected</td>
<td>Decreased 30% in TS</td>
<td>Unaffected</td>
<td>Not reported</td>
</tr>
<tr>
<td>(Glazc, Prost, &amp; Unaffectcd</td>
<td>Unaffected</td>
<td>Unaffected</td>
<td>Increased in TS</td>
<td>Reduced in TS</td>
<td>Not reported</td>
</tr>
<tr>
<td>(Jankovic &amp; Rohaidy, 1987)</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Reduced in TS</td>
<td>Not reported</td>
</tr>
<tr>
<td>(Drake M, Hietter, &amp; Bogner, 1992)</td>
<td>Decreased in TS</td>
<td>Prolonged in TS</td>
<td>Decreased in TS</td>
<td>Reduced in TS</td>
<td>Not reported</td>
</tr>
<tr>
<td>(Moeller &amp; Kreig, 1992)</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Unaffected in TS vs. Controls</td>
<td>Not reported</td>
</tr>
<tr>
<td>(Voderholzer, et al., 1997)</td>
<td>Decreased in TS</td>
<td>Not reported</td>
<td>Unaffected in TS vs. Controls</td>
<td>Unaffected in TS vs. Controls</td>
<td>Not reported</td>
</tr>
<tr>
<td>(Silvestri et al., 1995)</td>
<td>Decreased in TS</td>
<td>Prolonged in TS</td>
<td>Increased in TS</td>
<td>Decreased in TS</td>
<td>Reduced in TS</td>
</tr>
<tr>
<td>(Cohrs et al., 2001)</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Unaffected</td>
<td>Unaffected</td>
</tr>
</tbody>
</table>
Unfortunately, interpretation of data from these and other earlier studies is difficult because the majority of authors did not provide essential details about basic polygraphic variables, including total sleep time (Glaze et al., 1983; Drake M et al., 1992; Silvestri, De Domenico, & Di Rosa, 1990; Adrien, 1995). Study sample sizes were also rather small (two to nine patients), included wide ranges of age groups (e.g. 11-32 years) (Mendelson et al., 1980; Moeller et al., 1992; Silvestri et al., 1995; Voderholzer et al., 1997) and it is unknown whether patients awoke naturally or were awakened by the technicians in the morning. Allowing sleep ad lib is important when determining the total REM sleep time, because of the known circadian tendency for REM episodes to cluster in the last third of the night (Borbely, 1982).

A recent objective sleep study (polysomnographic) reported severity of TS was positively correlated with the number of nocturnal awakenings and sleep stage changes, and correlated negatively with sleep efficiency (Cohrs et al., 2001). No disturbances of REM sleep percentage, REM latency or overall total sleep time were observed in the 25 adult patients with TS. This study was flawed because only 13/25 patients were medication free during the polysomnographic study, while the other 12 were taking medications including neuroleptics and antidepressants, which are known to affect REM sleep (Wilson, Bell, Coupland, & Nutt, 2000). One patient used marijuana to self-medicate. Surprisingly, no sleep variables were found to be significantly different between medicated and unmedicated TS patients; nevertheless, pooling of the data for medicated and non-medicated subjects may not be justified and weakens the conclusions. Cohrs et al (Cohrs et al., 2001) reported increased tics and other motor movements during REM as well as non-REM sleep in patients with TS, and suggested this phenomenon may be attributable to a state of hyperarousal and possibly the reduced intracortical inhibition of motor pathways observed in TS. It is understood that REM sleep and nonREM sleep sequences are generated by reciprocal firing of monoaminergic and cholinergic pathways (Hobson, McCarley, & Wyzinski, 1975), and, while cholinergic neurons are responsible for the majority of
the components of REM sleep, the monoaminergic system is responsible for the nonREM sleep and for the inhibition of the cholinergic neurons (Sakai, 1984). Various movements during sleep have been described in patients with TS, e.g., REM sleep behaviour disorder (Trajanovic et al., 1997) and periodic limb movement disorder (Voderholzer et al., 1997). In a retrospective polysomnographic sleep study, REM sleep behaviour disorder was more common in TS patients than controls (Trajanovic et al., 1997). Phasic EMG twitching, and abnormally persistent or increased muscle tone and excessive leg movements during REM sleep periods characterized this disorder.

It is believed that the two aminergic transmitters, serotonin (evidence has been shown for decreased activity in TS) (Cohen, Shaywitz, Caparulo, Young, & Bowers, 1978) and norepinephrine (NE) (increased activity in NE in TS has been shown in these neurons that are believed to modulate the effects of dopamine) (Cohen et al., 1979)) share associations with both sleep regulation and TS pathophysiology (Adrien, 1995; Leckman et al., 1997). The interactions between norepinephrine and serotonin have been demonstrated by Cohrs (Cohrs et al., 2001) who reported a significant positive correlation between TS severity and the increased number of nocturnal awakenings, sleep stage changes and reduced sleep efficiency. This was consistent with the inverse correlation between tic severity and cerebrospinal fluid (CSF) concentrations of tryptophan (a precursor to serotonin) reported by Leckman et al. (Leckman, Goodman, Anderson, & et al., 1995). Based on this association, it has been suggested that both tics and insomnia in patients with TS may be due to reduced serotoninergic activity (Leckman et al., 1995). Moreover, the overall sleep in many of the TS patients is considered less restorative given increased number of awakenings observed (Stepanski, Lamphere, Badia, & et al, 1984),

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1 REM sleep behavior disorder (RBD) is described as the absence of somatic motor paralysis (excluding the diaphragm and extraocular muscles) during REM sleep. This atonia maybe a protective phenomena in that it prevents one from physically acting out his/her dreams. (Mahowald & Thorpy, 1995)
and it has been suggested that those with TS may be more irritable during the awake hours because of compromised sleep "quality" (Cohrs et al., 2001).

**Sleep Problems in ADHD**

Just as in TS, many relevant methodological issues have not been adequately addressed in previous sleep studies of children with ADHD although there is consensus that sleep disturbances are frequently associated with ADHD (Barkley, 1990). It is still unclear which components of sleep may be disrupted.

*Objective Sleep Studies*

In a recent review of sleep problems in children with ADHD (Corkum, Tannock, & Moldofsky, 1998), of the 9 studies reporting REM sleep variables, 4 described no differences in total REM minutes between Controls and the ADHD group (Palm, Persson, Bjerre, Wlmqvist, & Blennow, 1992; Stahl, Orr, & Griffiths, 1979; Feinberg et al., 1974; Small, Hibi, & Feinberg, 1971), 3 reported less REM in ADHD than Control children (Ramos Platon et al., 1990; Greenhill, Puig-Antich, Goetz, Hanlon, & Davies, 1983; Nahas & Krynicki, 1977) and 2 observed longer REM sleep latencies in children with ADHD compared to children without ADHD (Busby, Firestone, & Pivik, 1981; Haig, Schroeder, & Schroeder, 1974). Besides conflicting results, comparison of data between studies is difficult due to differences in diagnostic criteria, medication usage among the subjects and inadequate control procedures for age and pubertal maturity. The issue of controlling for subject age and pubertal maturity is critical because of known developmental changes in sleep architecture (Coble et al., 1987), and therefore has been addressed in the design of the current study.

*Subjective Sleep Studies*

The largest subjective study of sleep in TS + ADHD to date was reported by Allen et al (Allen, Singer, Brown, & Salam, 1992) who collected sleep questionnaires on a total of 146 boys
7 to 14 years of age. Of this group, 57 had TS only, 21 had ADHD only, 89 had both TS and ADHD and the balance were age-matched controls. They found the overall rate of sleep problems of the controls to be 9.7%, whereas 26.3% of the TS population and 41.4% of the TS with comorbid ADHD group reported sleep disturbances. These results suggested that the greatest risk of sleep difficulties was to be found among patient with both TS and ADHD. The validity of the conclusions is limited by a number of methodological problems, among them using a subjective measure of sleep disturbances, no control for medication, including only male subjects and a diagnosis of ADHD based on one 14-item questionnaire. Nevertheless, these findings were similar to those by Comings and Comings (Comings & Comings, 1987).

Corkum’s literature review of sleep and ADHD (Corkum et al., 1998) concludes that the majority of studies to date suffer from small sample sizes, inconsistent diagnostic criteria and procedures and the inclusion of only limited, if any, objective measures of sleep. She also noted that sleep disturbances in children with ADHD had yet to be compared to other clinical groups without comorbid ADHD, except for a single study (Marcotte et al., 1998), which relied on parental reports. Overall, there is very limited objective information available about the sleep parameters in TS, ADHD and the combination of the two disorders. Available studies provide information that is compromised by methodological problems (e.g. controlling for medication, age, gender, and pubertal maturity development; using single-night polysomnographic study without considering “first night effects”; and failing to rigorously screen for comorbidity). Only with these methodological problems clearly addressed could one begin to try to discern whether there is an association between specific sleep disturbances in these populations of children and maladaptive daytime behaviour.
Neurochemical Associations

Neurotransmitter Indications in TS

Studies involving rats and mice that had been placed in isolation for extended periods have been viewed as possible animal models of TS. Behaviours emerging after the rodents had been in seclusion included increased aggression, compulsiveness, hyperactivity, increased muscle tone, increased vocalizations, irritability, learning defects and hyper-responsiveness to stress (Valzelli, 1973). In these experimental mice, neurochemical changes also occurred, including a decrease of dopamine in the frontal lobes and an increase of dopamine in the nucleus accumbens and striatum. It was also observed that the isolated animals demonstrated an increased susceptibility to stress, similar to the increase of motor and vocal tics observed during times of stress and excitement in patients with TS. This pattern, interestingly induced by environmental changes, was very similar to what Comings et al. (1990) described as the “two syndromes of TS”. The first, a frontal lobe syndrome, results from too little dopamine, and includes behavioural features, e.g., aggression, anger, anxiety, motor and vocal tics, hyperactivity and insomnia. The second, a motor and vocal tic syndrome, is explained as an over activity of the dopamine neurons of the nucleus accumbens and striatum causing involuntary motor movements and vocalizations. This hypothesis has been supported by Parkinson’s Disease (PD) research, where affected patients have developed similar involuntary movements and vocal tics to those observed in TS, subsequent to treatment with L-DOPA (which increases levels of dopamine in the substantia nigra and ventral tegmental nucleus (Sacks, 1983; Shapiro & Shapiro, 1988).

Primarily TS is considered a movement disorder, with a focus on the motor tics. This constellation of symptoms has more recently directed a great deal of interest toward the basal ganglia as a possible site of altered brain function (Anderson et al., 1999), with increased central
dopaminergic transmission and possible disturbances of other neurotransmitter systems (Shapiro, Shapiro, Young, & Feinberg, 1988; Singer, Hahn, & Moran, 1991; Anderson et al., 1999). Advances in basal ganglia research have confirmed the significant role for dopamine (DA) in controlling output from the basal ganglia (Graybiel, 1990). It is understood that the development of motor and vocal tics in TS reflects increased dopaminergic activity due to postsynaptic dopamine receptor supersensitivity (Sandyk, 1995; Leckman & Peterson, 1993; Singer, Butler, Tune, Seifert, & Coyle, 1982). This observation is based on the well documented decrease in symptoms of patients with TS after treatment with dopamine receptor antagonists (Jankovic et al., 1984; Moldofsky & Sandor, 1988; Sallee, Nesbitt, Jackson, Sine, & Sethuraman, 1997). It has been demonstrated that haloperidol, which blocks postsynaptic dopamine receptor activity, reduces motor tics in over 50% of cases, while dopamine agonists e.g. L-dopa and methylphenidate (which stimulate postsynaptic dopamine receptors) have been shown to sometimes increase both the frequency and intensity of motor tics (Bruun, 1984; Messiha, 1988).

Singer and Walkup (Singer & Walkup, 1991), suggested that a biochemical abnormality occurring within the basal-ganglia thalamocortical (BGTC) pathway could produce symptoms of TS. Additional proposed models offering support for involvement of the BGTC underlying TS symptoms have linked a) the tics to disinhibition of the sensorimotor circuit (fibres from the sensorimotor cortex to the putamen) (Leckman et al., 1997; Miguel et al., 1997) b) the highly emotional component of some of the more complex motor and vocal symptoms with involvement of the limbic BGTC circuit and c) the repetitive behaviours observed in OCD symptoms to the orbitofrontal and limbic BGTC loops including the prefrontal cortical regions and the caudate nucleus (Leckman et al., 1997). Taken together, although there appears to be a good understanding of the general architecture of the BGTC circuitry, it is clear that the fine details and distinguishing aspects of each of the circuits requires further investigation (Parent & Cicchetti, 1998).
Extensive immunohistochemical studies of the basal ganglia in patients with TS have revealed a wide spectrum of differently distributed classic neurotransmitters, neuromodulators and neuropeptides (Graybiel, 1984; Parent, 1990). Specifically, mesencephalic monoaminergic (dopaminergic, noradrenergic and serotonergic) projections that modulate the activity of the corticostriatothalamocortical (CSTC) circuits have been repeatedly implicated in both TS and OCD (Leckman et al., 1993). The neurotransmitters are among those found in the motor cortex and basal ganglia, and, not surprisingly, subserve the same neuroanatomical structures involved in the initiation and execution of involuntary movements. It has been hypothesized that excessive DA input or tone could lead to the basal ganglia circuits being overly responsive and responding too quickly to commands. This could also lead to the involuntary vocal and motorics present in TS (Rogeness, Javors, & Pliszka, 1992). In contrast to the phenomenon observed in Parkinson's Disease (PD), where underactive dopamine neurons in the striatum produce muscle rigidity, decreased spontaneous movement and tremors, when dopamine neurons of the substantia nigra pathway are overactive, it is believed that this results in the unwanted, jerky movements present in TS (Comings, 1990). Also, additional behavioral domains of the basal ganglia include aspects of motor control, formulation of strategies and responses and the establishment and selection of emotional response sets (Saint-Cyr, Taylor, & Nicholson, 1995), each of which behaviours is often compromised in the clinical population of TS.

Finally, of the few autopsy studies reported in patients with TS one reported a remarkable total absence of the "external segment of the globus pallidus normally immunoreactively positive for the dynorphin A neuropeptide" (Haber, Kowall, Vonsattel, Bird, & Richardson, 1986). With this lesion it has been suggested that any number of the cortico-basal ganglia-thalamocortical circuits may be affected which could result in an increase in OCD behaviours (Saint-Cyr et al., 1995).
Ultimately, both the neuroanatomy and the specific neurochemistry of TS are not yet well understood and require further investigation. The following sections provide brief summaries of some of the most recent hypotheses of the role of the main neurotransmitters (NTs) believed to be involved in the observed symptoms and behaviours of TS.

**Dopamine (DA)**

All NTs have mechanisms for self-regulation, e.g., the availability and effectiveness of the NT at the synapse could be affected by precursor availability, synthesizing enzymes, metabolic enzymes, release and reuptake of the NT at the synapse and pre- and postsynaptic receptor functions (Rogeness et al., 1992). In the central nervous system (CNS) (Coyle, 1985) of the approximately 30 known NTs, the three which appear to be most involved in the regulation of the interaction of the child with the external environment (Antelman & Caggiula, 1977), and that have been most thoroughly studied in TS include norepinephrine (NE) dopamine (DA) and serotonin (5HT) (Leckman et al., 1997). The majority of evidence has indicated a primary dopaminergic dysfunction in TS (Brett, Curtis, Robertson, & Gurling, 1995), including fibres from the substantia nigra to the striatum and those that run from the ventral tegmental area to the frontal cortex (Leckman et al., 1997; Singer et al., 1991). The evidence for involvement of serotonin has been stronger in OCD research than in TS however, both disorders are closely related and are posited to share a common and underlying 5HT and DA abnormality (Comings, 1995).

High dopamine (DA) levels are believed to be associated with behaviours that involve increased motor activity, low motivation, increased aggressive behaviour and high levels of inappropriate sexual behaviour (Rogeness et al., 1992). The neurotransmitter norepinephrine (NE) with 5HT appears to be important in regulating the DA dependent behaviour, and NE with support from 5HT is thought to be important in attending to and assessing the
environment. Based on what is known about the functions of these systems, hypotheses have emerged regarding the dysregulation of these neurochemicals and the postulated relationship to maladaptive behavioural patterns (Rogeness et al., 1992). Sandyk et al (Sandyk & Bamford, 1987) proposed that imbalances in 5HT and monoaminergic systems could also be contributing to the high number of sleep disorders reported in TS patients.

In the TS population, increased activity of the DA system is considered a major contributor to the pathogenesis of the disorder. This hypothesis is based on data showing that the pharmacological agents that decrease DA function reduce tics, and those that stimulate DA receptors tend to exacerbate the symptoms (Leckman, Riddle, & Cohen, 1988).

Serotonin (5-hydroxytryptamine, 5HT)

The serotonergic neurons of the raphe nuclei project throughout the brain with particularly high density observed in the limbic areas and basal ganglia. It is understood that these pathways provide a route for influencing motor behaviours and related compulsive behaviours (Anderson et al., 1999). The frequent association between obsessive-compulsive behaviour and TS has also served to increase interest in 5HT in TS. There has also been evidence supporting a relationship between noradrenergic function and TS (Cohen, Delar, Young, & Shaywitz, 1980) including benefits from treatment with the serotonin (5HT) precursor 5-hydroxytryptophan (van Woert, Rosenbaum, & Enna, 1982) and the increasing number of studies noting the clinical relationship between TS and OCD (Anderson et al., 1999). The serotonin metabolite found in CSF, 5-hydroxyindole-acetic acid (5HIAA) was found to be low in some studies of TS patients (Butler, Koslow, Seifert, Caprioli, & Singer, 1979; Cohen et al., 1979; Leckman et al., 1988), and plasma tryptophan was low in another (Leckman, Anderson, & Cohen, 1984). A correlation between lower levels of 5HIAA and higher levels of HVA (the dopamine metabolite homovanillic acid) with weak neuropsychological scores in TS subjects has also been reported (Bornstein & Baker, 1988). This finding provided support for the hypothesis
of dysregulation of both dopaminergic (being high) and low serotonergic function in the TS population and its relationship to wider behavioural problems, rather than just tics (Bornstein et al., 1988). It is well recognized that there is a considerable amount of interaction between the dopaminergic and serotonergic neurotransmitter systems. Results from electrophysiological and neurochemical studies on rodents have generally shown that 5HT exerts an inhibitory influence on midbrain dopamine cell bodies (Kelland & Chiodo, 1996; Kapur & Remington, 1996), whereas 5HT influence over DA release in terminal regions has been less clear, having both inhibitory and excitatory effects.

Serotonin was originally associated with TS based on its influence on behaviour. Neurochemical studies have suggested decreased serotonergic function in TS although the evidence collected to date is not as clear as for increased dopaminergic function. It is understood that serotonergic function has a moderating, inhibitory effect on dopaminergic function; therefore increased serotonergic activity may be able to modulate some of the dysregulation of the DA system. In contrast, compromised serotonergic activity could cause a decreased ability to balance increased DA activity and therefore could result in a more severe expression of TS symptoms (Rogeness et al., 1992) and coincidentally, emergence of OCD symptoms. Conversely, the decreased serotonergic function in TS patients could be reflective of a compromised ability to compensate for elevated dopaminergic activity, therefore also resulting in a greater severity of TS symptoms (Rogeness et al., 1992).

**Serotonin and Aggressive behaviour**

Studies indicate that there is a positive correlation between low serotonin activity and aggressive behaviour in prepubertal boys (Pine et al., 1997). Children and adolescents with disruptive behaviour had decreased serotonergic function, and lower CSF 5HIAA levels than groups of children with OCD (Kruesi et al., 1990). Consistent with that, in a double blind,
placebo controlled study, treatment with fluoxetine (a selective serotonin reuptake inhibitor (SSRI), significantly reduced impulsive, aggressive behaviour (Coccaro & Kavoussi, 1997a). The association between decreased serotonin activity and an increased propensity towards aggressive behaviour is found in animal studies where compromised central serotonin functioning has led to impaired inhibition of responses required to wait or withhold responses (Mehlman, Higley, & Faucher, 1994). It has been reported that developmentally early dopaminergic (DA) lesions resulted in hyperactivity in rats (Shaywitz, Shaywitz, Cohen, & Young, 1984), which further led to changes in 5HT receptor sensitivity (Snyder, Zigmond, & Lund, 1986). Halperin (Halperin et al., 1997) investigated the relationship between age and 5HT function in aggressive and nonaggressive boys, and concluded that in contrast to normal development where 5HT function increases with age, aggressive children do not undergo an increase in 5HT function. It was recommended by the authors that a control group of children, and more rigid assessment for comorbid disorders (e.g., ADHD) was necessary to help clarify the relationship between neurochemical and behavioral factors. Low serotonin has also been correlated with increased aggression in adults and hyperactive children (Linnoila et al., 1983; Brown, Goodwin, & Ballenger, 1979). Similarly, animal studies have implicated the lack of the 5-HT1B receptor with increased aggressive behaviour (Sandou, Amara, & Dierich, 1994). Several studies have investigated the role of monoaminergic NTs, particularly serotonin (5-HT) in mood, anxiety disorders, and other forms of psychiatric dysfunction.

Neurotransmitter systems other than 5HT have also been represented as playing an important role in the manifestation of aggression (Raleigh & McGuire, 1980). It has been suggested that serotonin (5HT), norepinephrine (NE), dopamine (DA) and acetylcholine (ACh) may all be involved in the initiation and maintenance of aggressive behaviour in animals and humans (Young, Albin, & Penney, 1989; Parent, 1990). It could be hypothesized that in the TS population the serotonin system may be compromised, leading to impairment in impulse
control, increasing the likelihood of reacting to minor provocation with rage outbursts or aggressive behaviours. In addition to the relationship between reduced CSF 5HIAA levels and impaired impulse control, high CSF free testosterone concentrations have been associated with aggressiveness (Linnoila, Virkkunen, George, & Higley, 1993), leading to the hypothesis that in combination, these biological factors could lead to a predisposition for increased impulsive aggression and violent behaviour (Evenden, 1999).

5-HIAA and Aggressive Behaviour

Serotonin is metabolized into 5HIAA. Therefore 5-HIAA, an indicator of extracellular turnover of central serotonin (5-HT), is often used as a measure of serotonin (Bernhardt, 1997). An inverse relationship was reported between CSF levels of 5-HIAA and a variety of externalizing behaviours, e.g., the degree and frequency of violent acts in adults with a history of aggressive conduct disorder (Brown et al., 1985), and other behavioural problems, e.g., excessive alcohol consumption and polysubstance abuse (Moss, Yao, & Panzak, 1990). In a 2-year prospective study of children with disruptive behaviour, CSF levels of 5HIAA were lower and inversely correlated with measures of aggressive behaviour, e.g., repeated rule infractions (Kruesi et al., 1990). High scores on scales of psychopathic deviance (Brown et al., 1979), and increased risk-taking behavior and impulsivity (Mehlman et al., 1994) have also been associated with low levels of 5-HIAA in young males (Coccaro et al., 1997a). In contrast, Castellanos et al., (1995) reported a positive correlation between CSF 5-HIAA and aggression in boys with ADHD. The differences between various studies have been posited to reflect varying age groups, different severities of aggressive behaviour and the presence/absence of inattentiveness of hyperactivity in the children with ADHD (Halperin et al., 1997). The role of the 5HT system in aggression remains to be elucidated.

Although it is understood that peripheral measures (urinary metabolites) of 5-HIAA cannot directly access the CNS turnover of 5-HT, many studies have used peripheral measures
(such as urinalysis) because of the invasive procedure required to obtain CSF samples. It has been suggested that collecting CSF samples from children for other than medical purposes may actually be considered unethical (Bornstein et al., 1988). As a result, most of the data describing the relationship between biochemical variables (CSF 5HIAA) and aggression have been obtained from studies in adult populations (Birmaher et al., 1990).

Urinary 5HIAA has been used as a proxy for CNS turnover, and, although the majority of 5HIAA is believed to come from peripheral sources (e.g., platelet and gastrointestinal) it has been proposed that since peripheral measurements of NE metabolites are understood to be a proportional reflection of CNS turnover of NE, such an association is reasonable to assume with 5HIAA (Garvey, Noyes, Woodman, & Laukes, 1995). Results using urinary 5-HIAA, similar to CSF 5-HIAA levels, have been mixed. While older studies found no differences in urinary levels of 5-HIAA between children with minimal brain dysfunction and healthy controls (Sarrias, Cabre, Martinez, & Artigas, 1990), more recently, low urinary 5-HIAA levels were reported in violent adolescent offenders (Matykiewicz, La Grange, Vance, Wang, & Reyes, 1997) and a negative correlation with measures of overt aggression was found (Cetin, Cilden, & Burkovic, 1996). There have also been indications of sleep dysfunction associated with low levels of 5-HIAA (Matykiewicz et al., 1997), and there is interesting evidence that early dopaminergic (DA) lesions which produced hyperactivity in rats (Shaywitz et al., 1984) led to changes in 5-HT receptor sensitivity (Snyder et al., 1986). Although it is unlikely that 5-HT is the only neurotransmitter involved in the mediation of aggressive behaviour, taken collectively, these various studies support possible serotonergic system involvement in increased impulsive, and/or aggressive behaviour.
Serotonin and REM Sleep

Increased serotonin levels have been found to enhance REM sleep (Barr et al., 1994), and in a recent review of the role of 5HT in the regulation of REM sleep, collective evidence strongly supported a regulatory role for serotonin in REM sleep (Monti & Monti, 2000). Various sleep difficulties have been commonly reported in TS patients (Nee et al., 1980), Moldofsky et al., 1974; Barabas et al., 1984; Jankovic et al., 1984; Sandor, 1993; Sandor, 1997), supportively, significantly low levels of total REM sleep have been observed in a recent sleep study with TS patients, suspected to have compromised serotonin levels (Trajanovic et al., 1997).

Serotonin and ADHD

The association between 5HT mechanisms in ADHD and behavioural problems has been less driven by pharmacological evidence and based more on the role of 5HT in impulsivity, aggression, activity, learning and memory (Anderson, 1993; Zubieta & Alessi, 1992). Early clinical trials reported low blood serotonin in children with ADHD (Wender, Epstein, Kopin, & Gordon, 1971; Coleman, 1971) while others found no significant differences compared to controls (Shaywitz et al., 1984; Rapoport & Ferguson, 1981). Unfortunately the number of subjects involved in these trials was small, and screening for other comorbidity was not included. However, it is interesting that all the children in the Coleman (1971) study had been institutionalized in the Rosewood State Hospital due to extreme aggressiveness, and those with the lowest blood serotonin levels were the most hyperactive of all the subjects. This suggests a possible relationship between increased pathology with lower levels of serotonin. More recent research examining CSF 5HIAA levels in ADHD has suggested relationships between increased impulsivity and aggression with low 5HIAA levels, but overall have produced very limited data, none of which have been replicated (Zubieta & Alessi, 1993).
Testosterone and TS

The onset of symptoms in TS patients usually occurs within the first ten years of life, suggesting a developmental disorder. Following puberty, there is often a gradual improvement or resolution of motor and vocal tics (Bruun & Budman, 1997; Leckman et al., 1998). Clinical observations support changes in symptom expression of TS after alterations in sex hormone levels, e.g., menarche, during menstrual cycle, when using oral contraceptives, after menopause and during pregnancy (Shapiro et al., 1988; Leckman & Seahill, 1990). Sex hormones have important effects on brain development and gender-specific differentiation of brain structures (Cohen et al., 1994). It has been reported that treatment with androgenic steroids tends to increase tics (Leckman et al., 1990) and converse occurred with antiandrogen therapy (Peterson et al., 1992). Based on the prepuberal age of onset of most tic symptoms in TS, Cohen and Leckman (Cohen et al., 1994) have suggested that the surges of testosterone and other androgenic steroids during the critical period of fetal development in males may be responsible for functional sexual dimorphisms that could predispose the boys to develop motor and vocal tics later on in their development. Based on similar considerations, it has been suggested that there may be an interaction between the gene for TS and sex hormone levels in TS (Kurlan, 1992). Overall though, the evidence remains rather weak.

Testosterone and Aggression

Difficulties with impulse control have been related to testosterone (T) levels. Gerra et al. (1996), reported one of the more sensitive indices of outward-directed aggressiveness in subjects with high levels of T to be "irritability". In fact, the younger subjects studied who had a high level of T displayed more "turned out" characteristics (extra-aggression) than those with T levels within normal range. In a recent review (Harris, 1999) studies suggested testosterone may be related to irritability (Brown & Davis, 1975), level of frustration tolerance, dominance (Gray,
Jackson, & McKinlay, 1991) or impulsivity (Gladue, 1991). Testosterone levels influence how the individual responds to both social and physical environments. It is interesting that slightly elevated levels of T during adolescence and young adulthood have been reportedly associated with a history of violent crime (Volavka, 1995), whereas Constantino et al. (1993) reported an absence of any significant differences in T levels between highly aggressive and non aggressive boys, aged 4-10 years. In fact, in the latter study the authors suggested that it was possible to view previously published elevated T levels in aggressive adolescents and adults as effects rather than causes of aggressive behaviour. More recently, Schaal et al. (Schaal, Tremblay, Soussignan, & Susman, 1997) reported in a retrospective assessment of aggressive behaviour in boys aged 6-13, that boys with a history of high physical aggression prepubertally (age 6-12) had lower testosterone levels at age 13 than boys without a history of aggressive behaviour. Furthermore, suggestions have been made that aggressive, or dominance seeking behaviour, may be exacerbated if combined with low levels of serotonin, the latter which has been shown to make animals hyperresponsive to adversive stimuli and potentionally aggressive, thus increasing the likelihood for aggressive responses to frustrating events (Bernhardt, 1997). Support for these findings has been documented in animal studies, which describe increased levels of dominant, not aggressive behaviour in otherwise non-dominant adult rats when T levels are increased (Bonson, Johnson, Fiorella, Rabin, & Winter, 1994). Additionally, these dominant effects were reversed with the administration of a serotonin agonist, suggesting that high testosterone levels in conjunction with low levels of serotonin were related to dominance-seeking behaviour, not overt aggression. Scarpa Scerbo (Scarpa Scerbo & Kolko, 1994) found significant positive relationships between T and aggression scores, and no relationship between T scores and cortisol in aggressive children. It was interesting that across the 40 children studied, the levels of hormones did not differ between groups (diagnosis of Conduct Disorder (CD)), Oppositional Defiant Disorder (ODD) or ADHD but, only the presence of disruptive behavior (i.e., the specific
behavioural symptoms) among the individual children correlated with higher levels of $T$. Higher salivary $T$ scores have also been associated with the presence of learning disabilities in both boys and girls (Kirkpatrick, Campbell, Wharry, & Robinson, 1993). It is of interest that lower bioavailable testosterone ($T$) levels have been associated with sleep disorders (i.e., sleep disordered breathing) independent of the age of the subjects (Schiavi, White, & Mandeli, 1992).

Preliminary data on testosterone levels in 22 male TS patients randomly collected in the context of clinical work, indicated the TS males had significantly higher levels of Free Testosterone during early pubertal maturity than normative data suggested, however during and after pubertal maturity, when age normative ranges of $T$ are expected to increase considerably, the TS patient levels were significantly lower than age matched normal levels (Sandor, Stephens, unpublished, 1999). See Table 2.
Table 2. Comparison of Testosterone levels between Randomly Selected Clinical TS Patients and Normative Data

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Age (Group mean)</th>
<th>Free Testosterone Level n/u (Group Mean)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male TS patients</td>
<td>6</td>
<td>11.4</td>
<td>2.16 n/u</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Male Controls</td>
<td></td>
<td></td>
<td>&lt;.07 n/u</td>
<td></td>
</tr>
<tr>
<td>Male TS patients</td>
<td>8</td>
<td>14.4</td>
<td>31.54 n/u</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Male Control data</td>
<td></td>
<td></td>
<td>55-114 n/u</td>
<td></td>
</tr>
<tr>
<td>Male TS patients</td>
<td>8</td>
<td>36.6</td>
<td>47.22 n/u</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Male Control data</td>
<td></td>
<td></td>
<td>66-142 n/u</td>
<td></td>
</tr>
</tbody>
</table>

The lower levels of T in the adult males with TS did not seem to have an effect on fertility or development of secondary sexual characteristics. Thus, there is evidence, albeit preliminary, to suggest that young male TS patients have abnormally low T levels that in some individuals never reach developmentally normal adult T levels.

There has been an increasing interest in the multidisciplinary approach to studying the interaction among biosocial and psychological factors over the course of development in patients with TS and related disorders, the result of which has illuminated aspects of the normal developmental process as well as advancing our understanding of TS (Cohen and Leckman, 1994). As stated by Freedman (1992) “the study of developmental neuropsychiatric conditions challenges the practice of separating mind and mental processes (as defined by psychology), from brain and biological mechanisms, by reassembling mind and body into one person”.

40
Neuropsychological Profile of Tourette's Syndrome

Children and adults with TS are consistently reported as having a normal distribution of intelligence (i.e., mean = 100; standard deviation = 15) despite methodological differences and variations in tests administered (Como, 1993), but often experience academic difficulties and disruptions in cognitive functioning. A number of separate investigations have suggested a wide range of non-specific learning deficits (Schultz, Carter, Scahill, & Leckman, 1999; Cohen, Friedhoff, Leckman, & Chase, 1992a). There have also been reports of difficulties with written arithmetic computation and spelling skills (Stefl & Rubin, 1985; Bornstein, 1990); significantly higher Verbal IQ than Performance IQ (Bornstein, King, & Carroll, 1983; Shapiro et al., 1988); no discrepancy between Verbal and Performance IQ (Bornstein, 1990); weaknesses in attention and concentration (Golden, 1984; Kurlan, Whitmore, Irvine, McDermott, & Como, 1994); and deficits in visual-spatial-motor abilities (Como, 1993; Bornstein, 1990). Quite frequently problems with psychomotor speed and visual motor processing have been attributed to the presence of ADHD symptoms and the severity of motor tics (Como, 1993).

ADHD, OCD, sleep difficulties and aggressive behaviour are commonly found among children with TS, along with perceptual and cognitive difficulties. Neuropsychological difficulties can often be more problematic for academic progress and social development than the hallmark motor and vocal tics associated with this disorder (Cohen et al., 1992a). One study controlled statistically for the effects of tic severity and Obsessive Compulsive symptoms (Yeates & Bornstein, 1994) and found children with TS plus ADHD had lower scores than children with TS alone on measures of attention, including encoding (Digit Span) (Wechsler, 1991), focusing/executing (Trail Making Test), and sustaining attention (Speech Sounds Perception Test (Reitan, 1958)). Other studies have supported disorders of attention as “cardinal features” in people with TS, and have associated the severity of TS with the severity of attention problems (Randolph, Hyde, Gold, Goldberg, & Weinberger, 1993). The neuropsychological evidence that
TS subjects have impaired visuomotor integration skill and executive functioning in the presence of comorbid conditions such as ADHD and OCD, was recently reviewed (Schultz et al., 1999). Only a limited number of published studies on the neuropsychology of TS have controlled for confounding effects of co-existing ADHD and/or OCD. However there was one study attempting to tease out the ADHD "effect" which examined sustained attention and impulsivity in separate groups of children in contrast to comparable single diagnosis control groups (Sherman, Shepard, Joschko, & Freeman, 1998). Although sample sizes were relatively small (21 with TS only, 14 with TS + ADHD), results indicated that a diagnosis of TS did not significantly increase the risk of attentional problems in the absence of comorbid ADHD. Notably, although the children with TS only scored within normal ranges on tests of sustained attention, they demonstrated some impairment on measures of inhibition of impulsivity. These weaker scores were directly related to tic severity, consistent with the theory that TS without comorbidity involves dysfunction in cortical-subcortical circuits involved in mediating behavioural inhibition (Sherman et al., 1998). The high prevalence of additional disorders within the TS population makes it challenging to describe a "TS specific" neuropsychological profile. More recently, the recognition of these difficulties has led to attempts to control for these additional diagnoses in both the study design and data analysis (Spencer et al., 1998; Cirino, Chapieski, & Massman, 2000).

Original studies of domains of neuropsychological functioning in children with TS were compromised by small sample sizes and a primary focus on traditional IQ subdomain scores and on tests of visuomotor integration (e.g., Bender Gestalt Visuomotor test, Bender, 1938). More recently the emphasis has been on so called Executive Functions (EF), which usually includes measures of sustained attention and impulse control; planning, organization and cognitive flexibility; visuomotor integration and a variety of academic difficulties and learning disorders. Neuropsychological studies have also examined skills of EF in children with TS, (Baron-Cohen,
Cross, Crowson, & Robertson, 1994; Ozonoff, Strayer, McMahon, & Filloux, 1994; de Groot, Yeates, Baker, & Bornstein, 1997) although the findings have been inconsistent due to confounding comorbidity, in particular ADHD. Overall, when comparing previous neuropsychological studies of children with TS, methodological problems frequently emerge, including inconsistent diagnostic criteria for TS and comorbid conditions and the use of clinically referred samples that are usually more severely afflicted with TS and frequently have additional psychopathology. Given the wide range of severity and variety of comorbidity associated with TS, the neuropsychological profile of only clinically referred children is not likely representative of the TS population as whole (Schultz et al., 1999).

Both OCD and ADHD have specific neuropsychological markers. For example, children with ADHD alone usually present with a variety of EF deficits (Barkley, 1998) in comparison to children with pure OCD who tend to have more difficulties with visuoperceptual processes (Hollander et al., 1993; Zielinski, Taylor, & Juzwin, 1991). Investigations in TS have been focused on visuomotor integration and its components, i.e., visual perceptual skills, fine motor coordination, motor inhibition and sustained attention (Schultz et al., 1998; Schuerholz et al., 1996). The area of visuospatial deficits in TS has been investigated to a lesser degree (Bornstein, 1990; Dykens, Riddle, Hardin, Schwartz, & Cohen, 1990; Braun et al., 1993; Schultz et al., 1999).

**Executive Functioning**

In both neuropsychology and cognitive psychology, the definition of EF is provisional and under-specified, acknowledging how little is known about this area of cognition. In cognitive psychology EF is that part of cognition which logically must occur after perception and before an action is taken. In neuropsychology, EF tasks are those that patients with frontal lesions tend to do poorly on, e.g., demonstrating difficulties with planning, inhibition of response and impulse control (Pennington & Ozonoff, 1996). More specifically, the non-motor
prefrontal cortex has largely been associated with programming, action initiation, regulation and goal directed behaviour (Luria, 1966) and the dorsolateral prefrontal cortex with both inhibition of internally generated impulses and working memory (Fuster, 1995).

The broad skill set referred to as “Executive Functioning” does not refer to a single ability, but rather to a range of functions, including planning, goal directed behaviour, maintenance of cognitive set and cognitive flexibility, impulse control, sustained attention and effort, and self regulation. EF has been defined as “…the ability to maintain an appropriate problem-solving set for attainment of a future goal (Bianchi, 1922; Luria, 1966). The “problem solving set” can involve one or more of the following: a) an intention to inhibit a response or to defer it to a later more appropriate time, b) a strategic plan of action sequences, or c) a mental representation of the task including the relevant stimulus information encoded into memory and the desired future goal state (Pennington et al., 1996). The concept of EF remains distinct from cognitive domains such as sensation, perception, and many aspects of language and memory, while overlapping with such areas as attention, reasoning, working memory and problem solving.

Executive functioning and TS

It is important to understand that inconsistencies found throughout the literature on EF in TS may be in large part due to the failure to carefully screen the children with TS for additional disorders, e.g., ADHD (Schultz et al., 1999). Neuropsychological reports on children with TS have indicated deficits in the area of self-regulation of behaviour and ability to generate goal-directed behaviour (Pennington et al., 1996). Despite the overwhelming support for poor EF performance in children and adults with TS (Bornstein, 1991) Sherman, Janzen, & Joschko, 1996; (Yeates & Bornstein, 1996) there have been several studies which failed to find such EF deficits (Bornstein, 1990; Braun et al., 1993). This can partially be attributed to neglecting to account for comorbid conditions and failure to control for use of medications within the samples (Shucard, Benedict, Tekok-Kilic, & Lichter, 1997). Insomuch as difficulties with sustained attention have been consistently documented in children with ADHD (Barkley,
Grodzinsky, & DuPaul, 1992; Grodzinsky & Diamond, 1992) on measures such as the Wisconsin Card Sorting Test (WCST) (Seidman, Biederman, Faraone, Weber, & Ouellette, 1997) and EF tests, e.g., Trail Making Test (Reitan, 1958), Stroop Test (Stroop, 1935), go-no-go and conflicting response tasks (Shue & Douglas, 1992), several authors have strongly implied that it is the presence of a comorbid disorder, (such as ADHD) that is the significant determinant of neuropsychological weakness in TS (Harris et al., 1995; Como, 1993; Schuerholz et al., 1996). Based on clinical experience, the author of this thesis agrees that children with ADHD and comorbid TS often perform weaker on tests of EF (particularly those requiring sustained attention) while in contrast, children with TS only frequently score higher than average on the untimed EF tests that require limited or no motor component (e.g., WCST). The continuous verbal feedback (be it negative or positive) provided to the subject during this type of test appear to motivate the child with TS to continue, rather than evoke frustration and termination of the task, the response frequently observed in children with ADHD.

From a different perspective, in a recent study, the finding of impairment of the capacity to shift sets was postulated to be the result of serotoninergic dysfunction (Hollander & Wong, 1996). These findings suggest a variety of EF deficits may exist in children with lower serotonin levels (Barr et al., 1998). In view of evidence reviewed earlier that 5HT function is disturbed in TS, one may expect EF deficits in TS and even more so in TS + OCD. In conclusion, it has been suggested that future studies carefully examine comorbid psychopathology, developmental history, clinical phenomenology and family genetic history (Schultz et al., 1999) to better distinguish the groups of children with TS alone and TS + ADHD, in an effort to more clearly understand the impact of attentional problems on the executive functioning of children with TS, and the differences, if any, between these children and those with TS alone.
Executive functioning and aggressive behaviour

Cognitive-neuropsychological testing of aggressive and non-aggressive boys aged 6-12 years (Seguin, Pihl, Harden, Tremblay, & Boulerice, 1995) indicated that highly aggressive boys had significantly lower scores on tests of executive functioning (the ability to initiate and maintain efficient attainment of goals) than non-aggressive controls. These tests examined programming and planning of goal-oriented motor behaviour skills, modulation of behaviour in anticipation of future consequences, inhibition of response set and flexibility (vs. perseveration), the ability to use feedback cues, problem solving, and sustained attention (Petrides, Alvisatos, Meyer, & Evans, 1993). A secondary deficit area commonly associated with aggressive behaviour includes weaker verbal skills (receptive listening, reading, expressive speech, memory for verbal material) (Moffitt, 1993).

Executive Functioning and ADHD

In a review examining the relationship of EF to developmental psychopathologies, Pennington et al. (1996) found children with ADHD were fairly consistent in exhibiting poorer performance on measures of EF and vigilance/perceptual speed, with normal performance on most tests of verbal and non verbal skill. There were significant group differences between ADHD and controls in the majority of studies with the greatest consistency of EF impairment reported on specific measures, including: Tower of Hanoi (Planning) (Welsh, Pennington, Ozonoff, Rouse, & McCabe, 1990), Stroop (Inhibition) (Cohen & Servan-Schreiber, 1992b), Trails B (Set-shifting) (Reitan, 1958) and measures of motor inhibition. Interestingly, two of the studies explored the ability of cognitive tests to discriminate ADHD from learning disabilities (Robins, 1992) or developmental disorders (Weyandt & Willis, 1990), and found that cognitive tests are better at excluding normal children from the ADHD category than confirming ADHD in children as diagnosed by adult report. In a review (Pennington et al., 1996) it was suggested that the majority of children with a preliminary diagnosis of ADHD demonstrated deficits on
the cognitive tests, however the minority of children who scored within average range may actually be demonstrating ADHD symptoms for other reasons, e.g. comorbid TS. Across ADHD samples in 18 separate studies consistent deficits in EF tasks were reported with particular difficulties noted in motor inhibition and some general cognitive inefficiency (Pennington et al., 1996). These data suggest that the following tests of EF, Tower (subtest of the NEPSY) (Korkman, Kirk, & Kemp, 1998), STROOP Colour and Word test (Stroop, 1935), Trails B (Reitan, 1958), and a test of motor inhibition (e.g., Walk-Don’t-Walk) (Manly, Robertson, Anderson, & Nimmo-Smith, 1999) may be best suited to the task of examining certain aspects of EF in TS with and without ADHD.
Chapter Two

Rationale

The review of the literature leads to the proposition that reduced REM sleep may induce a state of hyper-responsiveness to dopaminergic stimulation (Tufik, 1998). Since TS is associated with a predisposed elevated dopaminergic tone, and there is some evidence of compromised REM sleep in this population, it could be hypothesized that the combination of decreased REM sleep and elevated dopaminergic tone in TS patients may be contributing to an increased risk of manifesting aggressive behaviour. Furthermore, low serotonin and suggested elevated testosterone levels reported in the prepubertal TS population indicate that this population may be at increased risk for the incidence of impulsive, frustration-related, aggressive behaviour due to neurochemical dysfunction. Finally, both low serotonin levels and above average levels of aggressive behaviour in children have previously been associated with weak scores on tests of EF, therefore I hypothesize a model in which I would expect to find low serotonin and high testosterone levels in prepubertal children with TS who a) exhibit high levels of aggressive behaviour, b) perform poorly on tests of executive functioning and c) have reduced percentages of REM sleep relative to their total sleep time. The objective of this thesis is to investigate the relative contribution of REM sleep, serotonin levels, testosterone levels, and executive function to daytime aggressive behaviour in children with Tourette’s Syndrome and associated behaviours.
Hypotheses/Research Questions

The primary objective of this thesis was to study the sleep architecture of children with Tourette’s Syndrome and to examine the following hypotheses:

1. The group of children with Tourette’s Syndrome will have a lower percentage of REM sleep than the group of Normal Healthy Controls
   a. The ADHD group will show lower percentages of REM sleep than the TS only group
   b. The TS + ADHD group will show lower percentages of REM sleep than TS or ADHD only

2. **REM Latency** will be significantly longer in all three diagnostic groups compared to Normal Healthy Controls

3. The children and adolescents who meet clinical levels of aggressive behaviour (regardless of diagnostic group) will have a lower percentage of REM sleep than the non-aggressive subjects

4. The children and adolescents with higher levels of testosterone than the comparison group will be rated as more aggressive by parents and teachers

5. The children and adolescents with significantly lower levels of serotonin than the comparison group will be rated as more aggressive by parents and teachers

6. People who do poorly on tests of Executive Functioning tend to have difficulty with inhibition of a prepotent response, therefore it is hypothesized that the children with significantly high levels of aggressive behaviour (demonstrating weak impulse control) will do poorly on tests of Executive Functioning compared to non-aggressive children
7. Children and adolescents who demonstrate a combination of: significantly lower percentage of REM sleep, increased REM latency, high testosterone levels and lower serotonin levels than normal healthy controls will be at increased risk of being rated as aggressive by parents and teachers.

**Inclusion Criteria:**
- Males and Females, ages 6 – 16 years
- Diagnosis of Tourette’s Syndrome according to DSM-IIIIR and/or a Diagnosis of Attention Deficit Hyperactivity Disorder according to DSM-IV (American Psychiatric Association, 1994)
- Healthy controls
- A good command of the English Language
- Able and willing to cooperate with the study protocol
- Medication free

**Exclusion Criteria:**
- Evidence of Pervasive Developmental Disorder, seizure disorder, severe head trauma, Post Traumatic Stress Disorder, Depression, known sleep disorder
- Estimated IQ below 80

**Study Design and Sample:**

The study design was case-control where a Healthy Control (HC) group was compared to 3 groups: Tourette’s Syndrome (TS) only, attention-deficit hyperactivity disorder (ADHD), and both TS and comorbid ADHD (TS + ADHD). The primary outcome variable was percentage of REM sleep in relation to total sleep minutes. Initial analysis of the data was performed using a one-way analysis of variance (ANOVA) to test for significant differences between the four groups on this variable.
Planned Comparisons

Calculations using 20 patients per group suggest that it will be possible to detect significant differences between two of the groups, but unlikely for multiple comparisons between all four groups, with only 20 patients per group. With four groups, there are 3 degrees of freedom associated with the F-test for differences between groups. Hence, a maximum of three (Cohen, 1992) comparisons between groups could be made. The 3 planned comparisons of interest were the following:

Healthy Controls vs. TS group,
TS group vs. TS + ADHD group, and
ADHD group vs. TS + ADHD group

Determination of Sample Size

To calculate the minimum sample size required to detect significant differences between diagnostic groups in REM sleep variables with adequate statistical power, an estimate of anticipated effect size was required (and the standard deviation of error terms for the population under investigation should be known). Following an extensive literature search, it was clear that such estimates could not be gleaned from existing empirical research findings due to small sample sizes, which fail to provide for accurate estimates of the standard deviation of error terms. The problem was further complicated by marked differences in research methodology among existing studies.

Instead, it was decided that a clinical-relevance criterion be adopted, with $\Delta / \sigma$ (the difference in means measured in units of the population standard deviation) equal or greater

\footnote{DSM-III-R diagnostic criteria are considered more appropriate for research purposes because of the inclusion in DSMIV of “disturbance causes marked distress or significant impairment in social, occupational, or other important areas of functioning” (Freeman, Fast, & Kent. 1995).}
than 1.25 necessary to demonstrate a clinically relevant effect. Using this criterion, with Type I error rate set at 0.02 (to correct for multiple comparisons), four equal-sized groups, and \(1 - \beta = 0.80\), approximately 18 participants were required per group (Neter, Wasserman, & Kutner, 1990). With twenty participants in each group, a 10% attrition rate is accounted for. Therefore the proposed sample size was 20 participants in each of the four groups, for a total sample size of 80. A similar conclusion could have been reached by following the recommendations of Cohen et al. (1992) if a medium-to-large effect size was anticipated.

Subjects

Ethics Approvals:

This study received joint ethics approval from the University Hospital Network Ethical Committee for Research in Human Subjects and the University of Toronto Office of Research Services Student Education Ethics Review Committee prior to the recruitment of subjects.

(Appendices)

Recruitment and Consent Procedures

Recruitment success rate was 94% of children invited into the study. Five subjects who declined to participate cited conflicting timetables, and/or inclement weather when scheduling the sleep study dates. Of the 80 children (and their parents/guardians) who agreed to participate, all completed the study.

Parents/guardians of prospective participants in this study were given an information letter describing the rationale and procedures of the study, and copies of the consent/assent forms for their review. After review of this material, parent/guardians who wished more information or wished to participate with their child(ren) in this study, were asked to contact the
author directly to make the necessary arrangements. All children invited to participate in this study were medication free for a minimum period of six weeks prior to enrolment. Of the subjects who had previously been on medication trials, four (4) of the ten (10) TS+ ADHD children had tried 2 or more different medications, while only one (1) child of the six (6) children with TS only (16%) had been on more than one medication. The two children (TS + ADHD) who had had short trials of neuroleptics (risperidone and haloperidol) had discontinued the medications more than a year before the study. Medication history is summarized in Table 3.

Of all the participants in the study 58/80 (72.5%) were medication naïve.

Table 3. Summary of medication history of all subjects

<table>
<thead>
<tr>
<th>Type of Medication</th>
<th>Tourette's Syndrome</th>
<th>TS + ADHD</th>
<th>ADHD</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulants (e.g. Ritalin, Dexedrine)</td>
<td>6</td>
<td>10</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>SSRI's (fluoxetine, fluvoxamine)</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Clonidine</td>
<td>4</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neuroleptics (risperidone, haloperidol)</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total No. of subjects*</td>
<td>6*</td>
<td>10*</td>
<td>6</td>
<td>0</td>
</tr>
</tbody>
</table>

* Some subjects had a history of multiple medication trials

Children with Tourette's Syndrome (with and without comorbid ADHD) were recruited from the Tourette's Syndrome Clinic at the Toronto Western Hospital. The referring
psychiatrist at the TS Clinic established the diagnoses of TS and ADHD and ruled out OCD using a semistructured interview and a series of self administered questionnaires as well as direct examination of each child/adolescent in a standardized manner, and referred patients for sleep evaluation. Participants with ADHD only (no tics) were referred by community pediatricians and the Child Health Unit at the Toronto Western Hospital. Before enrolment in this study, the children’s referring physicians or pediatricians confirmed all diagnoses of ADHD. Healthy controls were recruited by word-of-mouth through employees of the Toronto Western Hospital, their respective friends and/or relatives. Detailed medical histories were taken before enrolment to screen for existing medical conditions. Interested participants were provided with, or mailed a package of information describing the study in detail, including a set of consent and assent forms, for them to read at their leisure.

Stringent clinical diagnoses based on instruments outlined below and a clinical interview, were used to separate subjects into four distinct subgroups (TS only, TS plus comorbid ADHD, ADHD only, and normal healthy controls) with 20 children in each subgroup. Diagnosis was confirmed with a rigorous semi-structured interview (Family Self-Report Questionnaire + The Schedule for Affective Disorders and Schizophrenia for School-Age Children Epidemiologic Version) (Orvaschel, 1995) conducted by a trained graduate student (RS). This interview is based on DSM-IV diagnostic criteria. The subjects were also carefully screened for existing emotional and behavioral disorders using the Child and Adolescent Symptom Inventory (Gadow & Sprafkin J, 1994; Gadow & Sprafkin J, 1995). This interview yielded information about presence or absence of any comorbid disorder, in particular Attention Deficit Hyperactivity Disorder (ADHD), Oppositional Defiant Disorder and anxiety. The Hyperactivity Index Score from the Conners Parent Rating Scale (Conners, 1982) was used to determine the severity of
ADHD. A score exceeding seventeen (17) is considered clinically significant. Tic severity was assessed by the author using the Yale Global Tic Severity Scale (YGTSS) (Leckman et al., 1989) and the Global Tic Severity Scale (GTSS). The GTSS rating is based on the child's history of tics over the past year and combined with current clinical observation. Table 1 presents subject characteristics as well as the percentage of children in each group who reached clinical levels of ADHD, subject tic severity and the presence of other comorbid disorders. In addition, the author completed a Global Aggression Severity Scale (GASS®), which combines the history of aggressive behaviour over the previous year with current observations by the clinician.

**Sleep Study**

All children/adolescents participated in overnight polysomnographic sleep study in the Sleep and Alertness Clinic sleep laboratory at the Department of Psychiatry, Toronto Western Hospital on two consecutive nights. Each child was accompanied by a parent or guardian. Polysomnography is the recognized and accepted technique for objective, quantitative assessment of sleep. The first night was deemed necessary for adaptation to a novel environment, the results of the second night were used for analysis. First night effects have been shown (e.g., increased sleep latency and decreased Stage 4 and REM sleep) in younger children (6-7 years), however successful adaptation occurs by the second night (Coble et al., 1987). The procedure involved standardized measurement of a number of physiologically relevant parameters, such as electroencephalogram (EEG), electro-occulogram and submental electromyogram during sleep hours to enable a diagnosis of sleep disorders. The montage also incorporated monitoring of respiratory rate, electrocardiogram, oxygen saturation, nasal air flow and muscle activity in the limbs.
Sleep study procedure

The participants were booked in pairs or triplets to attend the Sleep and Alertness Clinic of the Toronto Hospital, Western Division for one two-night sleep study. The majority of the bookings were arranged on consecutive Friday and Saturday nights to avoid interrupting school routines. For certain families the study dates were arranged on Saturday and Sunday nights to accommodate religious holidays.

The children were asked to arrive at the laboratory between 20:00 and 20:30 on each night of the study, accompanied by a parent or guardian. The sleep clinic is located within a self-enclosed wing in the Toronto Western Hospital, and includes three separate bedrooms, each equipped with two single beds (one for the child’s parent/guardian and one for the child). There was a common area (with TV/VCR, electronic games and movies for children’s entertainment), a washroom with a shower and a small kitchen. Efforts were made to make the children and their parents/guardians feel comfortable within the unfamiliar surroundings. One qualified female sleep technician (N.A.), was employed throughout the study for consistency, and she greeted the families in the evening, provided orientation to the facility, equipment and procedures, and confirmed informed consent and assent prior to initiating the study. Subsequently, the technician set up the computerized polysomnographic equipment. A series of small disc non-invasive electrodes were applied to the scalp and face with electrode cream and taped in place to record the electroencephalogram (EEG) from central (C3-A2 and C4-A1) leads, electrooculogram (EOG, right and left outer canthi) and electromyogram (EMG, submental), according to the standard criteria (Rechtschaffen & Kales, 1968). Leg movements, respiration and oxygen saturation were also monitored throughout the night. Recordings of
EEG, EOG and EMG allow us to identify the stages of sleep and determine sleep disturbances. Respiration belts were connected across the children’s upper rib cage and around the abdomen. Blood oxygen saturation (Sa02) was measured during sleep by applying an infrared light sensor to the child’s finger that measured arterial oxygen levels and monitored the children on video from an adjacent technician’s room. Children were allowed to sleep until they woke up spontaneously. Should the child have awoken during the night or very early morning, the parent/guardian and technician attempted to soothe the child and have them return to bed.

Sleep Record Scoring

A single experienced sleep technician (D.J.) who was blind to the diagnostic assignment, scored all the records. Standard sleep measures including sleep latency, wakefulness after sleep onset (WASO), total sleep time in minutes (TST), sleep efficiency, REM sleep latency (taken from sleep onset to the first appearance of REM), amount of REM sleep (minutes), REM density, distribution of REM and SWS across the nights, percentage of sleep stages 1, 2, 3, 4 of non REM sleep were assessed. The results from both nights were recorded, scored and reviewed, however only the second night was used for analysis.

Saliva and urine sample collection

Both mornings after the sleep study the children were asked to provide a saliva and urine sample. The saliva samples (about 2-3 ml), were consistently collected between 7:00 am and 9:00 am and frozen within one (1) hour for later analysis of salivary testosterone. Children were asked to ‘spit’ into a small paper cup, following a procedure reported in Harris et al (Harris, Rushton, Hampson, & Jackson, 1996):
"Saliva samples provide an accurate and reliable measure of the biologically active component of testosterone. Salivary testosterone consists essentially of the unbound portion of serum testosterone, since testosterone bound to sex hormone binding globulin does not pass through the salivary glands. Unbound testosterone is considered to be the bio-available fraction and represents approximately 2 to 3% of the total circulating testosterone (Pardridge & Demers, 1991). Salivary testosterone correlations with free testosterone in serum have been reported to fall between .93 (Navarro, Juan, & Bounin, 1999) and .97, for men and mixed-sex samples. Correlations of .80 and above have been reported in women (Smith, Besch, Dill, & Buttram, 1979)."

**Quantification of Salivary Testosterone:**

Samples were stored at -70°C until analysis. Concentration of testosterone in children’s saliva was measured by a specific testosterone RIA kit (Diagnostic Systems Laboratories, Inc., Webster, Texas) according to the modifications described by E. A. Granger et al. (Granger, Schwartz, Booth, & Arentz, 1999). The detection limit of the assay was 1 pg/mL (3.47 pmol/L). The within-run precision was 3% and between-run precision was 8%.

Secondly, the children were asked to provide a first morning urine specimen on each of the two mornings. They were asked to void, with the assistance of their parent if necessary, their complete first urine sample of the day into a clean, dry container. Parents and children were given instructions as to how to cleanse the external genitalia before voiding. The urine sample was used to estimate levels of serotonin.

**Quantification of Urine Serotonin:**

Urine samples (morning, random) were immediately acidified with 6N HCl (10ml/L urine) and stored at -70°C until analysis. Concentration of urine serotonin was measured with a specific enzyme immunoassay kit (Immuno-Biological Laboratories, Hamburg, Germany). In brief, serotonin was chemically derivatized to N-acylserotonin. The competitive assay of
biotinylated and non-biotinylated N-acylserotonin for anti-serotonin (rabbit) was performed in micro-well plates coated with anti-rabbit IgG. Bound biotinylated N-acylserotonin was measured by the use of anti-biotin alkaline phosphatase with p-nitrophenyl phosphate as substrate. The detection limit of the assay was 60 nmol/L of urine. The within-run precision was 7% and between-run precision was 15%.

**Neuropsychological Testing**

After breakfast following the first sleep study night, the children were asked to participate in approximately one hour of neuropsychological testing. An estimated General Intelligence Quotient was obtained using the Vocabulary, Information, Block Design and Picture Completion subtests (correlation .93 to .95 with full administration) of the WISC-III (Wechsler, 1991). Tests of Executive Functioning included the Wisconsin Card Sorting Test\(^1\) (Berg, 1948; Heaton, 1981; Heaton, Chelune, Kay, & Curtis, 1993), the “walk-don’t-walk” subtest of the Test of Everyday Attention for Children (Manly et al., 1999) (TeaCH), Test of Trail Making (A & B) (Parpington & Leiter, 1949; Reitan, 1958), the Stroop Color and Word Test, (Stroop, 1935) Semantic Word Fluency (Wiig & Semel, 1987), Letter Word Fluency (Benton & Hamsher, 1989) and either the Tower of Toronto (Saint-Cyr, Taylor, & Lang, 1988) or the Tower subtest of the

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\(^1\) The Wisconsin Card Sorting Test (WCST) is a widely used measure of EF shown to be sensitive to frontal lobe dysfunction in adults and children, although its specificity may be less robust than its sensitivity (Heaton et al., 1993). The participant is asked to sort 128 cards one at a time according to color, form, or number of shapes on the card, and is given feedback about the correctness of their response; the correct sorting category is changed after 10 correct responses, and continues until the subject appropriately “shifts set” 5 times. For the purpose of data analysis in this study, measures of the number of categories achieved, perseverative errors (T score) and perseverative responses (T score) were chosen as variables based on their frequency of use in previous literature (Cirino et al., 2000).
Neuropsychological Assessment of Children (Korkman et al., 1998) (NEPSY). The latter test was used for children up to and including 12 years 11 months of age.

Scale of Physical Maturity

The most well-known and accepted system with which to classify the degree of physical maturation in children and adolescents was described by Tanner (Tanner, 1962). However, assessment by this method requires a trained medical expert to examine the naked child in order to rate the amount of growth in breasts and pubic hair in females, onset or absence of menses, and in males, penis, scrotum and testicle development as well as pubic hair growth. While it is considered the most accurate for establishing the progression of secondary sexual characteristics, obtaining Tanner signs challenges both comfort level of many young subjects and acceptable ethical practices within the context of a research protocol. As an alternative, I elected to obtain estimates of pubertal level using the Self-Administered Rating Scale for Pubertal Development (Carskadon & Acebo, 1993). This scale correlates well ($r=.82$) with the complete Tanner sign physical examination, while it is less invasive. The children or adolescents were asked to respond to five multiple choice response questions describing their physical development. For the younger children parents completed the form, and assistance was offered to all subjects to ensure that the questions were understood correctly. Responses were scored according to the protocol 4 and scores assigned to the corresponding category depicting the approximate level of pubertal development of each child.

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4 Pubertal development was scored to within five (5) categories, based on the following self-reported factors: for the boys body hair, voice changes and facial hair; and for the girls body hair, breast development and menarche. Boys were considered prepubertal if they reported no development on any of the three characteristics or more development on one characteristic but no development on the other two. They were classified as midpubertal if they reported beginning development on all three or advanced development on one or two combined with little or no development on the others. Finally, they were considered late pubertal if they reported advanced development on all three or beginning development on one combined with advanced or completed development on another and completed development on the third. Finally, boys were classified as postpubertal if they reported completed development of pubic hair, facial hair and voice. Girls were considered prepubertal if
Family Environment

While their child was being tested, parents were asked to complete questionnaires (detailed below) describing their child's behaviour at home during the past two weeks, and to complete the adult version of the Picture-Frustration Test (Rosenzweig, 1978) based on their own responses to frustrating hypothetical situations. This semi-projective test is used for disclosing patterns of response to everyday stress that is indicative of both normal and abnormal adjustment. For the purposes of this study parent only responses were scored under one dimension, Direction of Aggression. This dimension can yield one of three categories, i.e., Extratraction (EA), in which aggression is turned onto the environment; Intratraction (IM) in which the subject turns aggression onto him/herself; and Intratraction (MA), in which aggression is evaded in an attempt to gloss over the frustration. More support has been generated for the validity of Directions than for Types of Aggression, the other main dimension scored with this instrument (Rosenzweig, 1998).

Behavioural scales

Parents/guardians completed psychometric measures indicating the presence or absence of aggressive behaviour\(^5\) at home and at school including the Achenbach Child Behavior Checklist (CBCL) (Achenbach, 1991) and the Conners Behavior Rating Scales (Conners, 1982).

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5 *Children's aggression* was measured using a variety of instruments including the Global Impression Anger Aggression Scale (GIASS; see Endnote) during the clinical assessment, and the Parent and Teacher forms of the Achenbach Child Behavior Checklist (CBCL)(Achenbach, 1979).

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Parents also completed the Eyberg Child Behavior Inventory (ECBI) (Eyberg & Ross, 1978). This brief paper and pencil behavioural rating scale of externalising or conduct problems in children aged 2 to 16 consists of 36 items assessing typical problem behaviours reported by parents. This measure correlates well with independent observations of children's behaviour to differentiate clinic-referred and non-clinic populations. Reliability coefficients for the ECBI scales range from .86 (test-retest) to .98 (internal consistency). The ECBI (and the complementary teacher version SESBI-R) are scored on two scales; one measures the frequency with which the child displays the behaviour and the other indicates how often the parent or teacher considers the behaviour a problem for him/herself.

**Completion of participation**

The child and their parents were permitted to leave the hospital Saturday morning after completing the neuropsychological testing, until 20:30 that evening, when they were asked to return for the *second and final night of the sleep study*. The final morning (Sunday), after providing urine and saliva samples, parents and children were free to go home.

**Teacher Reports**

Parents delivered *four questionnaires to the teacher* with a letter requesting that they complete the questionnaires and mail them back to the clinic in the provided postage paid pre-addressed envelope. Approximate time required to complete the questionnaires was twenty (20) minutes. These instruments included the Teacher Rating Scale (TRF) (Edelbrock & Achenbach, 1984), the Conners Teacher Rating Scale (CTRS) (Conners, 1982), the Child Symptom Inventory → (Teacher version) (Gadow et al., 1994) and the Sutter-Eyberg Student Behavior Inventory (SESBI-R) (Rayfield, Eyberg, & Foote, 1997).
STATISTICAL ANALYSES

METHODS

Descriptive statistics

Descriptive statistics provided an overview of the data. To test for a diagnostic group effect, analysis of variance (ANOVA) was used if the distribution was normal. If the overall group effect was significant, the 3 planned comparisons were tested with contrasts between the group pairs listed in the previous section. If the distribution was not normal, the nonparametric test of Kruskal-Wallis was used to test for significant differences between the 4 groups. Categorical variables were tested using chi-square. If the Pearson chi-square statistic was not valid, due to having expected counts less than 5, the likelihood ratio chi-square test was used.

Testing for differences

Testing for differences between the first and second night sleep parameters was done using paired t-tests. This method allowed each patient to use the first night result as his or her own baseline for testing differences between the 2 nights.

Classifying patients into aggressive or non-aggressive was based on the parent and teacher version subscales of Aggressive behaviour on the Achenbach Child Behavior Checklist (CBCL) and corresponding Teacher Report Form (TRF). For determining clinical levels of aggressive behaviour, the aggression subscale scores were converted to age-corrected T-scores. To examine the clinically significant aggressive behaviour the children were categorized as follows. For each individual T-score derived from the teacher or parent reports equalling to or exceeding a T=67 6, the subject was assigned a score of 1. If their T-score fell below the cutoff

6 A categorical cutoff of T=67 is recommended for statistical purposes to significantly discriminate between referred and nonreferred children on the problem subscales of the Achenbach scales (Achenbach, 1991, p. 57).
of T=67, the subject was assigned a zero (0) from that rater. Subjects were grouped as Non-Aggressive if their total combined score equaled zero (0) (non-aggressive across both venues); Aggressive (if their score totaled 1; aggressive in one venue), or Very Aggressive (a score of 2; rated aggressive by both parent and teacher). The frequency of each category of aggressive behaviour severity was examined in each diagnostic group. Further analysis examined the relationship between aggressive vs. non-aggressive children and the pre-determined outcome variables (e.g., percentage REM sleep, REM latency, serotonin and testosterone levels, tests of Executive Functioning).

Pearson's correlation coefficients

Pearson's correlation coefficients between each of the sleep parameters and the CBCL and TRF aggression subscale scores for parent and teacher were estimated for the entire sample and for each diagnostic group. Similar analysis was performed to test the linear relationship between the CBCL aggression subscale score and the Brief-Anger-Aggression questionnaire. Additional correlations were estimated for the relationship between sleep parameters and aggression scales, neuropsychological tests, testosterone and serotonin levels.

Only patients with tics (TS only and TS+ADHD groups) were analyzed to determine whether there were significant relationships between tic severity, sleep parameters and presence or absence of clinical levels of aggression. Analysis of variance tests determined whether there were differences between levels for the sleep parameters and aggression scales.

Justification for multivariate analyses

When a group manifests abnormal findings in two or more measures, this does not necessarily imply that any causal relationship exists between the two variables, or that the classification variable determining group membership is the reason for those elevations. For
example, a researcher may find sleep abnormalities, increased aggression, and neurotransmitter abnormalities in individuals with a particular clinical diagnosis (compared to a control group), and create a model in which these variables are somehow causally related to the diagnosis and to one another.

Two variables may be related through a common though unknown cause, or alternatively because measurement error is correlated (Klem, 1995). It is also not the case that when two groups differ in the mean levels of two variables, that it is the classification variable determining group membership that caused the difference, because the observation may reflect differences among the groups in an important explanatory variable that is excluded from the analysis.

While experimental research avoids these problems by random assignment of cases to conditions, this is not always possible in a clinical investigation, of which the present study is an example (i.e., it is not possible to randomly assign children to different diagnostic groups). In this case, the most I can hope for is statistical control. In the previous analyses, an attempt was made to achieve statistical control with Multiple Linear Regression (MLR) analyses. However, as described in greater detail in the following section, MLR analyses are problematic due to specification errors that can result from incorrect or atheoretical model selection techniques.

The values of regression coefficients can vary drastically according to which other particular predictors are included in a given model, and are further complicated by the issue of multicollinearity. Even when using an ANOVA procedure, if experimental control has not been achieved in the research design, one is still subject to making specification errors by failing to enter the appropriate covariates. In order to address these issues, differences in groups was controlled statistically by employing multivariate analyses for the final phase of data analyses.
Analysis of Covariance (ANCOVA)

If differences were found among groups on demographic variables, Analysis of Covariance (ANCOVA) was used. The most valid application of ANCOVA involves the use of a covariate in statistical analyses to account for variance attributable to a concomitant variable. This reduces the magnitude of error variance if the concomitant variable is related to the outcome measure, at the cost of only one degree of freedom in the analysis, and makes the detection of treatment effects more likely (Neter, Wasserman, & Kutner, 1990). However, ANCOVA is also frequently employed in order to correct for biases or inequalities encountered in observational investigations, even though this application involves several questionable assumptions, and warrants a cautious and careful examination of the nature of the dataset.

One of the most fundamental assumptions in ANCOVA is that of equal slopes of the regression function describing the relationship between the concomitant variable and the outcome variable across the whole dataset (i.e., the slope of the regression function does not vary as a function of the treatment group variable). If this assumption is not met, the use of ANCOVA is obviously not valid (Neter et al., 1990). Accordingly, I tested whether the relationships between age, level of pubertal maturity, and each of the outcome measures was different among the diagnostic categories using MLR analyses. In order to accomplish this, I created indicator variables (through dummy coding) to represent each diagnostic category, and entered all these as predictor variables along with the concomitant variable (age or level of pubertal maturity) and interaction terms representing the product of the indicator variables and the concomitant variables (Neter et al., 1990). In these analyses, I was specifically concerned with the potential emergence of statistically significant interaction terms. If such interactions are found, it indicated that the slope of the regression function describing the relationship between
the concomitant variable and the outcome variable is different for a particular diagnostic group, compared to the control condition.

Another problematic issue with the use of ANCOVA to correct for biases in observational data involves the extrapolation (or interpolation) of regression functions describing the relationship between the concomitant variable (e.g., age; pubertal maturity) and outcome measures to a region in which there are few (if any) data points (Neter et al., 1990). One cannot be confident that the data in the extrapolated (interpolated) region conform to the same pattern as the regions for which data are observed.

In order to compensate for this problematic issue, strong inferences about group differences were restricted to outcome measures in which the raw (unadjusted) mean values for treatment conditions were consistent with a priori predictions, and in which the differences in the raw and covariate-adjusted values were not substantial.

Finally, the use of ANCOVA with observational data may be problematic when the treatment variable is causally related to the concomitant variable(s) or vice-versa. For example, if ADHD is conceptualized as resulting from a developmental or maturational delay, then the variables ‘age’ and ‘level of pubertal maturity’ are causally related to the variable ‘diagnostic category’. This problematic aspect of ANCOVA was addressed by the final set of data analyses by employing multivariate analyses (in the form of path analyses) to make causal inferences about the interrelationships among the observed variables in the investigation.

**Multiple Linear Regression Analyses**

MLR is a statistical technique that can be used to analyze the contribution of predictor variables to variance in a criterion or outcome variable (Licht, 1995; Neter et al., 1990). Through the use of hierarchical MLR analyses, a researcher can determine the independent and unique
contribution of a linear combination of predictors by examining the incremental increase in explained variance ($R^2$) as blocks of variables are added to a model (Neter et al., 1990). The contribution of individual predictor variables can also be determined through examination of partial regression coefficients. These coefficients represent the contribution to the criterion, when the effects of all other variables in the analysis are partialed out of both the predictor variable and the criterion variable.

In general MLR analyses do not have the capacity to determine the true underlying causal structure of the interrelationship between variables. However, if used in a manner informed by theoretical considerations, MLR can be a useful tool to investigate such relationships, and to exert statistical control over a set of variables in order to make inferences about a phenomenon when experimental control is not possible. Unfortunately, the use of MLR is fraught with logical and methodological pitfalls.

The complexity and difficulty of conducting theoretically meaningful MLR analyses increase when substantial relationships exist between predictor variables. This situation results in a phenomenon known as multicollinearity, the consequences of which include an increase in error variance, and unstable estimates of the regression coefficients. MLR analyses are most valid when conducted with a theoretical framework in mind (Pedhazur, 1982; Neter et al., 1990).

An even more problematic issue in MLR analyses is the manner in which relevant predictor variables are selected and entered into the analysis. Methods of variable selection such as forward entry, backward elimination, or stepwise regression are commonly used, but ultimately these methods rely on the empirical data at hand in order to select an optimal set of variables to serve as predictors for a given criterion variable (Licht, 1995). Data-driven analyses
conducted in such a manner are likely to capitalize on chance variation in the data, and are difficult to replicate when cross-validation is attempted in a separate sample. Furthermore, when predictor variables are selected in an atheoretical, data-driven manner, specification errors are likely to occur (Licht, 1995). A specification error occurs when an important explanatory variable is left out of the analysis. The values of all other MLR coefficients can vary dramatically when even one important variable is either included or excluded from the analyses. Thus, empirical selection of predictors is not likely to include all theoretically meaningful predictors, and often produces misleading and non-reproducible results. The best way to minimize the possibility of specification errors is to measure and select predictor variables according to well-established theory and prior empirical research (Licht, 1995; Neter et al., 1990).

The most useful technique for these purposes is hierarchical MLR analysis. With this technique, a researcher can create theoretically meaningful linear combinations of predictor variables, and determine the incremental increase in the amount of variance in the criterion that is explained when these linear combinations are entered consecutively as separate blocks in the analysis (Neter et al., 1990). The increase in explained variance ($\Delta R^2$) is tested for statistical significance, and indicates the amount of variance accounted for in a criterion (outcome measure) by a block of variables when other blocks of variables are already accounted for in the analysis.

If differences among the groups in aggression-related variables accounts for the differences in parent and teacher ratings of aggressive behaviour among groups, then one should expect diagnostic classification and aggression-related variables to account for overlapping variance in aggressive behaviour (i.e., shared variance). Thus, when accounting for
one set of variables in the model (e.g., diagnostic classification), including the other set of variables in analysis should not result in any significant increase in explained variance. Thus, this set of analyses tests the null hypothesis that testosterone, serotonin and sleep physiology variables will not account for any variance in parental and teacher ratings of aggressive behaviour after indicator variables representing the diagnostic groups have been already accounted for in the regression model. If the null hypothesis is rejected, the above mentioned variables account for a significant amount of variance in parental and teacher ratings of aggressive behaviour (after diagnostic classification has already been accounted for in the analysis), then the inference can be made that the two different sets of variables account for independent and unique variance in ratings of aggressive behaviour.

In order to answer these questions, hierarchical regression analyses were employed to examine the relative contribution of variables corresponding to diagnostic categories, and those reflecting other parameters related to aggressive behaviour. Examination of the incremental change in $R^2$ at each block indicated whether the linear combination of predictor variables entered into the model accounted for a significant portion of the variance in aggression ratings beyond that accounted for in the previous block of the analysis.

1) Variance in aggressive behaviour attributable to the participant’s age was accounted for in the first block
2) Variance in aggression related to 5HT/testosterone/EF was examined in the second block and finally,
3) Variance in aggressive behaviour accounted for by diagnostic classification; ADHD, TS, TS+ADHD, HC) was examined in the third block

Predictor variables reflecting physiological and cognitive factors related to aggressive behaviour were entered into the analyses in the second block. These factors are not necessarily specific to diagnostic groups, even though differences amongst the groups were demonstrated in
previous analyses for some of the variables. Three types of variables were entered in this second stage: those reflecting hormonal/neurotransmitter levels (serotonin, testosterone), those reflecting sleep function (percentage REM), and those reflecting inhibitory processes associated with response inhibition/frontal-lobe function (WCST Perseverative Errors).

This was accomplished by creating indicator variables for each category (through dummy coding), to avoid the problem of artificially forcing a metric on the diagnostic groups that would occur with the use of one categorical variable with four levels. The procedure of entering indicator variables to represent diagnostic classifications into MLR analyses is a procedure that yields results equivalent to those obtained from ANOVA, with the value of the regression coefficients indicating how much greater (or smaller) than the reference category (control group) is the effect of the particular diagnosis, in the units of the criterion.

Path Analysis

In order to address the problematic issue of model specification and the interrelationship between predictor variables, it was decided to adopt the multivariate analytical procedure of path analysis. Whereas MLR analysis is plagued by methodological problems such as intercorrelated predictor variables and multicollinearity (Pedhazur, 1982), path analysis allows one to specify a model in which the relationship between the predictor variables can be estimated, and thus the mediating and moderating influences of variables can be examined (Klem, 1995). In this way, path analysis allows for the calculation of indirect effects that a variable can have on outcome measures (effects mediated through other variables). Path analysis can be used to test hypotheses about the causal relationship between a set of observed variables, but like MLR, the technique is valid only when the models created are informed by theoretical considerations (Klem, 1995).
Chapter Three

Results

Part I: Descriptives including Comorbidity and Tic Severity

Eighty (80) children participated in this study, 20 of whom had a diagnosis of TS, 20 with TS plus ADHD, 20 with only ADHD and 20 healthy controls (HC). Table 1 presents demographic characteristics of the entire sample. During the K-SADS-E interview, parents of 7 subjects in the TS+ADHD group (35%), 6 children with ADHD (30%) and 1 child with TS only (5%) reported their children demonstrated behaviours falling within the Oppositional Defiant Disorder (ODD) spectrum. However, on examination of the specific items endorsed by the parents, it was found that the majority of items overlapped very closely with DSMIV associated features of ADHD. These included "low frustration tolerance", "temper outbursts", "bossiness", and "stubbornness" as described in the DSMIV description of ADHD associated features, in comparison to "touch/easily annoyed", "often loses temper", "defies adults requests" from the K-SADS-E interview. Subsequently, without the necessary additional diagnostic criteria information available (e.g. evidence of clinically significant impairment in social, academic or occupational functioning) a comorbid diagnosis of ODD could not be confirmed in these 13 subjects, thus an additional diagnosis was not made. Of the 80 children, 57 (71.25%) were male and there were no significant gender differences between groups. There were no significant group effects for Estimated IQ. There were highly significant differences observed using ANOVA for both the problem and intensity subscales of the Eyberg Child Behavior

\[\text{Estimated IQ based on four subscale scores of WISC-III (Vocabulary, Blocks, Information, Digit Span) (Wechsler, 1991)}\]
Inventory (Parent and Teacher versions) between the four subject groups (Parent Intensity subscale, p<.004, Parent Problems subscale, p<.002; Teacher Intensity and Problem subscales, p<.002) with the ADHD group rating higher on all subscales than the other three study groups, and the TS+ADHD Parental Problems subscale scores higher than the TS alone or Controls. Based on our planned comparisons using the Mann-Whitney test, Controls did not differ from the TS only group on either subscale as rated by both parents and teachers. TS + ADHD and the ADHD group were not significantly different as rated by parents and teachers. When comparing the TS only and TS+ADHD groups, only the Parent subscale of Problem Intensity was rated significantly higher for TS+ ADHD (mean 51.5, sd=6.62), than for children with TS only (mean 45.41, sd =11.24) (p<0.02).

The Conners Parent Rating Scale Hyperactivity Index8 scores (using age corrected normative scoring) were not normally distributed across all four comparison groups; therefore, the Kruskal-Wallis test was used to test for differences between the four diagnostic groups. There was a highly significant group effect (p=0.001) for degree of hyperactive behaviour. As expected, both the TS + ADHD (mean 23.2, sd= 7.24) and ADHD only groups (mean 28.05, sd=6.94) scored significantly higher for hyperactive behaviour than subjects with TS alone (mean 18.5, sd=10.6) (p<0.03) or Controls (mean 13.85, sd=4.57) (p<.0001). There was no significant difference in level of Hyperactive Behaviour ratings between the ADHD and TS + ADHD groups. (See Table 4.)

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8 Conners Parent Rating Scale (Conners, 1982)
There was an overall group effect for age (p < .007) with the Control group the eldest (mean=11.55, sd = 2.03), followed by TS only (mean = 11.15, sd= 2.2), TS plus ADHD (mean =9.75, sd= 2.07) and ADHD only (mean =8.8, sd = 2.14). Both the TS only and Control groups were significantly older than the ADHD group ( p <.002 and p< .001 respectively), and TS group was significantly older than the TS plus ADHD group ( p<.046). (TS plus ADHD and the ADHD only groups did not differ significantly in age.) (See Table 4)

**Table 4. Demographics and characteristics of participants ( N=80)**

<table>
<thead>
<tr>
<th>Diagnostic Group</th>
<th>TS only</th>
<th>TS + ADHD</th>
<th>ADHD only</th>
<th>Controls</th>
<th>Group Total</th>
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<tr>
<td>Subject Age</td>
<td>Mean</td>
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<td>9.75</td>
<td>8.80</td>
<td>11.55</td>
</tr>
<tr>
<td></td>
<td>Std Deviation</td>
<td>2.21</td>
<td>2.07</td>
<td>2.14</td>
<td>2.04</td>
</tr>
<tr>
<td>Estimated IQa</td>
<td>Mean</td>
<td>97.30</td>
<td>97.40</td>
<td>95.47</td>
<td>104.15</td>
</tr>
<tr>
<td></td>
<td>Std Deviation</td>
<td>13.82</td>
<td>14.37</td>
<td>12.90</td>
<td>14.65</td>
</tr>
<tr>
<td>Gender</td>
<td>no. (% male)</td>
<td>17 (85%)</td>
<td>14 (70%)</td>
<td>15 (75%)</td>
<td>11 (55%)</td>
</tr>
<tr>
<td>CPRS HIb</td>
<td>Mean</td>
<td>18.50</td>
<td>23.20</td>
<td>28.05</td>
<td>13.85</td>
</tr>
<tr>
<td></td>
<td>Std Deviation</td>
<td>10.16</td>
<td>7.24</td>
<td>6.95</td>
<td>4.57</td>
</tr>
<tr>
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<td>6</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>ADHD-Combined</td>
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<td>17</td>
<td>14</td>
<td>0</td>
<td>31</td>
</tr>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
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<td>Oppositional Behaviour</td>
<td>1</td>
<td>7</td>
<td>6</td>
<td>0</td>
<td>14</td>
</tr>
</tbody>
</table>

* a IQ based on four subscale scores of the WISC-III (Vocabulary, Blocks, Information, Digi Span)
* b Connors Parent Rating Scale Hyperactivity Index T-Score

Understandably, the distribution pattern of pubertal development stages resembled that for age. ANOVA revealed a significant overall group effect (p<.002). Using contrast, we discovered that the distribution of pubertal development was equally distributed in TS only, TS + ADHD, and Control groups, however, the ADHD alone group showed significantly less
mature pubertal development vs. the other three groups (p<.010, p<.043 and p<.001 respectively). See Table 5.

<table>
<thead>
<tr>
<th>Level of Pubertal Maturity</th>
<th>Diagnostic Group</th>
<th>TS only</th>
<th>TS + ADHD</th>
<th>ADHD only</th>
<th>Controls</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prepubertal</td>
<td>Count</td>
<td>8</td>
<td>10</td>
<td>16</td>
<td>3</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>% within</td>
<td>40.0%</td>
<td>50.0%</td>
<td>80.0%</td>
<td>15.0%</td>
<td>46.3%</td>
</tr>
<tr>
<td></td>
<td>Diagnostic Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early Pubertal</td>
<td>Count</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>7</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>% within</td>
<td>20.0%</td>
<td>20.0%</td>
<td>10.0%</td>
<td>35.0%</td>
<td>21.3%</td>
</tr>
<tr>
<td></td>
<td>Diagnostic Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mid Pubertal</td>
<td>Count</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>% within</td>
<td>20.0%</td>
<td>15.0%</td>
<td>10.0%</td>
<td>20.0%</td>
<td>16.3%</td>
</tr>
<tr>
<td></td>
<td>Diagnostic Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Late Pubertal</td>
<td>Count</td>
<td>4</td>
<td>2</td>
<td>.30</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>% within</td>
<td>20.0%</td>
<td>10.0%</td>
<td></td>
<td>30.0%</td>
<td>15.0%</td>
</tr>
<tr>
<td></td>
<td>Diagnostic Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post Pubertal</td>
<td>Count</td>
<td>.00</td>
<td>1</td>
<td>.00</td>
<td>.00</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>% within</td>
<td>5.0%</td>
<td></td>
<td></td>
<td></td>
<td>1.3%</td>
</tr>
<tr>
<td></td>
<td>Diagnostic Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>Count</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>% of Total</td>
<td>25.0%</td>
<td>25.0%</td>
<td>25.0%</td>
<td>25.0%</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Tic severity was measured in both the TS only and TS+ADHD groups using the Yale Global Tic Severity Scale. Of the 20 subjects with a diagnosis of TS only (group tic severity mean 1.25, sd=.55), 16 scored within the range for mild, 3 moderate and 1 severe tics. In the TS + ADHD group (group mean 1.70, sd = .73), 9 children scored within the range for mild, 8 moderate and 3 severe tics. See Table 6.

9 Based on Yale Global Tic Severity Rating Scale (Leckman et al., 1989)
Table 6. Tic Severity Ratings for TS and TS + ADHD (n=40)

<table>
<thead>
<tr>
<th>Diagnostic Group</th>
<th>TS only</th>
<th>TS + ADHD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yale Global Tic Severity Scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>16</td>
<td>9</td>
<td>25</td>
</tr>
<tr>
<td>% of Total</td>
<td>20.0%</td>
<td>11.3%</td>
<td>31.3%</td>
</tr>
<tr>
<td>Moderate</td>
<td>3</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>% of Total</td>
<td>3.8%</td>
<td>10.0%</td>
<td>13.8%</td>
</tr>
<tr>
<td>Severe</td>
<td>1</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>% of Total</td>
<td>1.3%</td>
<td>3.8%</td>
<td>5.0%</td>
</tr>
</tbody>
</table>

Because of small number of subjects, the moderate and severe tic levels were collapsed to form a moderate-severe category, and this group was compared to those with mild tic severity. Chi-square analysis revealed significant group differences indicating that TS+ADHD group included significantly more subjects with moderate-severe tic severity level (n=11) than those with TS alone (n=4) (p<.022). See Table 7.

Table 7. Mild and Moderate-Severe Tic Ratings by Diagnostic Group

<table>
<thead>
<tr>
<th>Tic Severity Rating</th>
<th>Mild tics</th>
<th>Mod-severe tics</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Diagnostic Group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TS only</td>
<td>16</td>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>TS + ADHD</td>
<td>9</td>
<td>11</td>
<td>20</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>15</td>
<td>40</td>
</tr>
</tbody>
</table>

* p<.022
Tic severity had no significant impact on sleep parameters or measures of aggression using ANOVA.

**Aggression Scores**

*Overall Aggression Scores by Diagnostic Group*

The nonparametric Kruskal-Wallis test was used to test for overall group differences on the Aggression subscale scores for both the parent and teacher versions of the Child Behavior Checklist (CBCL/TRF). The analysis was conducted using a non-parametric test because scores on this scale were not normally distributed. Analyses revealed a highly significant ($p < 0.001$) main effect for group. Further analysis using Mann-Whitney test indicated that both parents and teachers rated the TS + ADHD and ADHD groups equally in terms of aggressive behaviour. Upon comparing TS only and Controls, although teachers rated both groups equally for aggressive behaviour, only parents rated the TS group significantly more aggressive than Controls. The final comparison, TS vs. TS + ADHD revealed only borderline differences in aggressive behaviour as rated by parents ($p = .063$) and teachers ($p = .072$). Of note, fewer Teacher Report Forms than Parent Rating Scales were returned and available for analysis, because some of the subjects participated in the study during the summer holidays. (Table 8).
Table 8. Summary of planned comparisons between Diagnostic Groups of Parent (CBCL) and Teacher (TRF) Subscale of Aggression T-scores

<table>
<thead>
<tr>
<th></th>
<th>CBCL Aggression T-score (Parent)</th>
<th>N</th>
<th>Std. Deviation</th>
<th>TRF Aggression T-score (Teacher)</th>
<th>N</th>
<th>Std. Deviation</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TS vs.</strong></td>
<td>59.15*</td>
<td>20</td>
<td>12.77</td>
<td>56.07</td>
<td>14</td>
<td>9.63</td>
<td>p=&lt;.037</td>
</tr>
<tr>
<td>Controls</td>
<td>52.60*</td>
<td>20</td>
<td>4.89</td>
<td>52.78</td>
<td>19</td>
<td>4.46</td>
<td>p=&lt;.474</td>
</tr>
<tr>
<td><strong>TS vs.</strong></td>
<td>59.15</td>
<td>20</td>
<td>12.77</td>
<td>56.07</td>
<td>14</td>
<td>9.63</td>
<td>p=&lt;.063</td>
</tr>
<tr>
<td>TS + ADHD</td>
<td>63.70</td>
<td>20</td>
<td>10.07</td>
<td>61.22</td>
<td>18</td>
<td>10.30</td>
<td>p=&lt;.072</td>
</tr>
<tr>
<td><strong>TS + ADHD vs</strong></td>
<td>63.70</td>
<td>20</td>
<td>10.07</td>
<td>61.22</td>
<td>18</td>
<td>10.30</td>
<td>p=&lt;.473</td>
</tr>
<tr>
<td>ADHD</td>
<td>66.95</td>
<td>20</td>
<td>13.27</td>
<td>64.20</td>
<td>20</td>
<td>9.83</td>
<td>p=&lt;.312</td>
</tr>
</tbody>
</table>

Child Self-Report Anger and Aggression Scale

There was a significant linear relationship between the Brief Anger Aggression Questionnaire (BAAQ) completed by each child, and the CBCL aggression subscale completed by the parents (Pearson correlation r=0.56, p<0.001), as well the BAAQ and the similar subscale of Aggression on the Teacher rating form (TRF) (r=0.29, p<0.02) using the entire sample.
Parent Self-Report Responses

The Rosenzweig Frustration/Aggression self-report scale, which is a limited projective self-report test for assessing reactions to frustration that yields scores under two main dimensions: direction of aggression and type of aggression in adults, adolescents and children. In the context of the instrument, aggression is generically defined as assertiveness, which may be either affirmative or negative in character. For commenting on overall family aggressive behaviour in this study, we selected to examine the direction of parental aggression. More support has been generated for the validity of Directions than for Types of Aggression (Rosenzweig, 1998), which aided our decision to select this factor. Chi-square test indicated significant differences between all four groups (p<0.03). Planned comparisons using Mann Whitney tests for further analysis of the categorical variables, showed that parents of the TS only and TS + ADHD children differed significantly in terms of direction of aggressive behaviour (p<0.048). There was an even distribution of the three possible directions of aggression in the TS only group (5/5/5). In contrast, the majority of parents of children with TS + ADHD (12/18) scored within the Extraggresission category. This pattern was also reflected in parents of children with ADHD, with 12/18 parents scoring within the Extraggresission category. The distribution of responses was not significantly different between TS + ADHD and ADHD nor TS only and Controls. See Table 9.
Table 9. Rosenzweig Frustration Aggression Scale: Parent Direction of Aggression (n=80).

<table>
<thead>
<tr>
<th>Group</th>
<th>Rosenzweig Parent Aggression Direction</th>
<th>p-values for Planned Comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Extraggession</td>
<td>Intraggession</td>
</tr>
<tr>
<td>TS only</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>TS + ADHD</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>ADHD only</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Controls</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>27</td>
</tr>
</tbody>
</table>

Clinical Levels of Aggression: Additional Analyses

Including all subjects in the analysis for the measurement of aggressive behaviour is based on the assumption that aggressive behaviour is measured on a continuum, and significant differences between groups are meaningful without limitations or cutoff scores for clinical significance. Although the differences in levels of aggressive behaviour between groups are meaningful qualitatively, it is interesting to also investigate which groups had more children whose level of aggressive behaviour was rated by parents and teachers to reach clinical referral ranges. Therefore, to investigate whether the four study groups differed in the number of children who manifested clinically significant levels of aggressive behaviour, all subjects were classified into aggressive or non-aggressive groups based on parent and teacher Aggressive behaviour subscale T scores on the Achenbach Child Behavior Checklist (CBCL) and Teacher...
Report Form (TRF). After converting raw scores to age-corrected T-scores, each T-score ≥ 67
10 (teacher and/or parent report) was assigned a score of 1. If the T-score fell below the cutoff of T≥67, the subject was assigned a zero (0) from that rater. Subjects were grouped as Non-Aggressive if their total combined score (parent and teacher ratings) equaled to zero (0) (non-aggressive across both venues); Aggressive (if their score totaled 1; aggressive in one venue), or Very Aggressive (a score of 2; rated aggressive by both parent and teacher).

To answer the question of whether the groups differed at clinical levels of aggressive behaviour as perceived by parents and teachers, an overall Chi-Square analysis was conducted comparing the number of categorically non-aggressive, aggressive and very aggressive children across the four subject groups. Only three diagnostic groups remained in the analysis (TS, TS+ADHD and ADHD), as there were no subjects within the Control group with Aggression T scores on either scale reaching clinical levels (T≥67). Including the three remaining groups in the Chi Square analysis, there were no significant differences overall between the number of children rated as clinically aggressive by parents or teachers (p<.415, NS). Based on our planned comparisons using a 2 x 2 Chi Square test with diagnostic group and Parent/teacher rating of aggression greater than or equal to a T=67, it was found that parents of the ADHD group rated a significantly higher number of their children as clinically aggressive (10/20) than parents of TS only children (4/20) (p<.047). This pattern was not evident on the teacher rating scale. The number of children rated as clinically aggressive by both parents and teachers in the TS only (1/20) and TS + ADHD (4/20) groups did not differ significantly (p<.091 NS). There were also no significant differences between the number of children rated as clinically aggressive by

10 A categorical cutoff of T=67 is recommended for statistical purposes to significantly discriminate between referred and nonreferred children on the problem subscales of the Achenbach scales (Achenbach, 1991, p. 57)
both parents and teachers when comparing TS + ADHD (4/20) and ADHD children (4/20) 
(p<.752, NS). However, children who met clinical aggression levels across both venues (school 
and home) were significantly more represented in the both the TS+ADHD (3/20), and ADHD 
groups (4/20) than Controls (0/20) or TS alone (1/20) (p<.001). See Figure 1.

Figure 1. The number of subjects in each group with CBCL Aggression subscale scores 
exceeding the clinical cutoff score of T>67.

- Parent (CBCL)
- Teacher (TRF)
- Both

<table>
<thead>
<tr>
<th>Diagnostic Group</th>
<th>No. of children</th>
</tr>
</thead>
<tbody>
<tr>
<td>TS Only</td>
<td>3</td>
</tr>
<tr>
<td>TS+ADHD</td>
<td>9</td>
</tr>
<tr>
<td>ADHD</td>
<td>10</td>
</tr>
<tr>
<td>ADHD Controls</td>
<td>1</td>
</tr>
</tbody>
</table>

* p<.047 △ p<.001
* p<.04
Student T-tests Comparing Aggressive vs. Non-Aggressive Children

Student T-tests were performed comparing aggressive and non-aggressive children (as previously classified in the methodology above (p. 77) on the outcome variables used in this study. There were no significant differences in percentage of REM sleep, REM latency, serotonin and testosterone levels between categorically defined aggressive and non-aggressive children within each diagnostic group.

However, significant differences emerged (regardless of diagnostic category) on the neuropsychological subtest of the NEPSY (Tower) (T (58)=3.30; p<.002) emerged between children rated as clinically aggressive (group mean = 8.70; sd= 3.23) and non-aggressive (group mean = 11.38; sd=2.96), and on the WCST (perseverative errors; T (58) = 2.54; p<0.014) between aggressive (group mean = 43.26; sd = 13.10) and non-aggressive children (group mean = 50.0; sd=7.45) groups as a whole. On both tests, the groups with the significantly lower T scores (indicative of poorer performance) were the children displaying clinically aggressive behaviour.

For subsequent analyses, the WCST (perseverative errors) was included as our neuropsychological test outcome measure based on well-established psychometric properties (i.e., reliability and validity) in combination with the consistency of the form of the instrument across all age categories examined.

First and Second Night Sleep Study Data

The differences between the first and second sleep study night results are summarized in Table 10. Based on the paired t-test results, there were significant differences on a number of
variables including REM latency and percentage REM sleep. First nights in the sleep lab were considered acclimatization time to the surroundings and the procedures. Both nights of sleep data were used for secondary analyses. Only the second night data from each child’s polysomnographic sleep study were used for all subsequent analysis.

Table 10. Summary of paired t-test values for differences between Night 1 and Night 2 (Re: Select sleep study parameters, testosterone and serotonin levels) (N=77)

<table>
<thead>
<tr>
<th></th>
<th>Day 1 mean</th>
<th>Day 2 mean</th>
<th>Mean Difference</th>
<th>Std. Deviation</th>
<th>Sig. (2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>REM Latency</td>
<td>149.23</td>
<td>119.47</td>
<td>29.76</td>
<td>64.30</td>
<td>.000</td>
</tr>
<tr>
<td>%REM Sleep</td>
<td>16.38</td>
<td>19.99</td>
<td>-3.61</td>
<td>5.04</td>
<td>.000</td>
</tr>
<tr>
<td>Sleep-onset (min)</td>
<td>23.06</td>
<td>12.44</td>
<td>10.62</td>
<td>17.28</td>
<td>.000</td>
</tr>
<tr>
<td>Total sleep (min)</td>
<td>434.72</td>
<td>505.28</td>
<td>-70.56</td>
<td>76.90</td>
<td>.000</td>
</tr>
<tr>
<td>Sleep-efficiency %</td>
<td>87.39</td>
<td>95.00</td>
<td>-7.60</td>
<td>11.57</td>
<td>.000</td>
</tr>
<tr>
<td>WASO(^1)</td>
<td>8.56</td>
<td>2.49</td>
<td>6.06</td>
<td>11.90</td>
<td>.000</td>
</tr>
<tr>
<td>%Stage 1</td>
<td>5.41</td>
<td>5.03</td>
<td>.38</td>
<td>2.37</td>
<td>ns</td>
</tr>
<tr>
<td>%Stage 2</td>
<td>40.15</td>
<td>43.82</td>
<td>-3.66</td>
<td>8.73</td>
<td>.001</td>
</tr>
<tr>
<td>%Stage 3</td>
<td>5.60</td>
<td>5.38</td>
<td>.21</td>
<td>2.43</td>
<td>ns</td>
</tr>
<tr>
<td>%Stage 4</td>
<td>23.18</td>
<td>22.46</td>
<td>.71</td>
<td>5.75</td>
<td>ns</td>
</tr>
<tr>
<td>Total awakenings</td>
<td>13.06</td>
<td>11.21</td>
<td>1.85</td>
<td>7.3</td>
<td>.032</td>
</tr>
<tr>
<td>Total SWS (min)(^2)</td>
<td>131.94</td>
<td>140.84</td>
<td>-8.90</td>
<td>37.04</td>
<td>.041</td>
</tr>
<tr>
<td>REM sessions</td>
<td>4.01</td>
<td>4.76</td>
<td>-.74</td>
<td>1.28</td>
<td>.000</td>
</tr>
<tr>
<td>Total leg movements</td>
<td>25.36</td>
<td>22.22</td>
<td>3.13</td>
<td>24.70</td>
<td>ns</td>
</tr>
<tr>
<td>Total arousals</td>
<td>48.33</td>
<td>53.86</td>
<td>-5.52</td>
<td>18.88</td>
<td>.014</td>
</tr>
<tr>
<td>Arousals from SWS(^3)</td>
<td>3.85</td>
<td>4.24</td>
<td>-3.36</td>
<td>2.56</td>
<td>ns</td>
</tr>
<tr>
<td>Testosterone pg/ml</td>
<td>19.83</td>
<td>18.84</td>
<td>.994</td>
<td>9.93</td>
<td>ns</td>
</tr>
<tr>
<td>Serotonin nmol/L</td>
<td>177.84</td>
<td>221.27</td>
<td>-43.42</td>
<td>87.89</td>
<td>.000</td>
</tr>
</tbody>
</table>

\(^1\)Wakefulness After Sleep Onset (%)
\(^2\)Total Slow Wave Sleep minutes

Part II: Group Differences: Sleep Parameters and Aggressive Behaviour

The slopes of the regression functions describing the relationship between the concomitant variables (age; pubertal maturity) were not different among the diagnostic groups
for most of the outcome variables examined. Exceptions to this occurred with the variables REM latency and Stroop interference score. Thus, ANCOVA was not be employed for analyses examining group differences when these two variables are involved, nor was it used in any subsequent multivariate analyses, to avoid the risk of introducing artifact into the results.

In order to determine the best independent and unique predictors of aggressive behaviour, Stepwise MLR analyses was conducted using parental ratings and teacher ratings as criterion variables. ADHD diagnosis alone, ($\beta = 0.52; p < 0.001$) and with TS co-morbidity, ($\beta = 0.28; p < 0.01$), response inhibition (WCST perseverative errors), ($\beta = -0.34, p < 0.001$), and Day 2 5-HIAA levels ($\beta = -0.26; p < 0.01$) emerged as significant predictors of parental ratings, while ADHD diagnosis alone ($\beta = 0.48$), and with TS co-morbidity ($\beta = 0.28$) was the only significant predictor of teacher ratings of aggressive behaviour.

**REM Sleep Latency and Percentage REM sleep**

ANCOVA was performed on second night sleep lab data for 77 subjects (second night data on three subjects was not available due to technical failure). Significant main effects of diagnostic group on REM sleep latency, the first of our main outcome variables, was revealed using subject age and pubertal level as covariates ($p<.029$). Then upon further analysis for group differences, contrast results on planned hypothesis testing revealed that the ADHD group had significantly longer REM sleep latency (mean 147.34 min, sd=42.52) than the TS + ADHD group (mean 109.57 min, sd=47.07) ($p<.012$). Our second main outcome variable, Percentage of REM Sleep, was also significant for diagnostic group using ANCOVA controlling for age and pubertal level ($p<.037$). Planned comparisons revealed Control subjects had a significantly higher percentage of REM (mean = 21.68 sd=4.35) than TS alone (mean 19.43, sd=2.41)
19.43, sd=2.41) (p<.045) and the TS +ADHD group had a significantly higher percentage of REM sleep (mean=20.74, sd=4.18) than the ADHD group (p<.031) See Figure 2.

Figure 2. Second Night Percentage of REM Sleep and REM Latency by Group (covariates of Age and Pubertal Level of Maturity) n=77

"=" p< 0.45  "=" p< 0.031  "=" p< 0.012
Additional Sleep Parameters

ANOVA revealed an overall group effect on sleep parameters including total sleep minutes (p<0.05), total slow wave sleep (p<0.02), and total arousals (p<0.009). Specifically, ADHD children recorded significantly more total sleep minutes (mean 529.5, sd=48.74)(p<0.02) than all three comparison groups: TS (mean 497.7 sd=35.51, p<.023) TS plus ADHD (mean 497.8, sd=50.6, p<.023) and Controls (mean 495.05, sd=31.6,p<.016). Both groups with ADHD (ADHD and TS + ADHD) had significantly longer SWS than Controls (p<.03).

Interestingly, both the TS + ADHD group (mean 4.95, sd=2.5) and the ADHD group (mean 5.05, sd=2.6) had significantly more arousals during SWS than the TS group (mean 3.35, sd=2.1)(p<.030 and p<.023 respectively). A marginally higher number of movements during SWS was also shown for both TS + ADHD and ADHD compared to Controls (mean 3.57, sd=1.7) (p<.06 and p<.051 respectively) while the TS group did not differ significantly from the Control group. Number of movements during REM sleep sessions was marginally higher for ADHD than all three other comparison groups (p=0.06). Apart from the number of arousals from slow wave sleep, no other significant differences were found when comparing sleep parameters of TS only and TS + ADHD groups. See Table 11.
Table 11. Sleep parameter Group Differences (Night 2) (n=77)

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>TS-Only</th>
<th>TS + ADHD</th>
<th>ADHD</th>
<th>Overall Mean</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 19</td>
<td>n = 20</td>
<td>n = 20</td>
<td>n = 19</td>
<td>N = 78</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M (SD)</td>
<td>M (SD)</td>
<td>M (SD)</td>
<td>M (SD)</td>
<td>M (SD)</td>
<td></td>
</tr>
<tr>
<td>% REM sleep</td>
<td>21.68(4.35)*</td>
<td>19.43(2.41)*</td>
<td>20.74(4.18)*</td>
<td>18.25(2.38)*</td>
<td>20.01(3.61)*</td>
<td></td>
</tr>
<tr>
<td>REM Latency</td>
<td>98.11(34.25)</td>
<td>121.39(40.93)</td>
<td>106.67(47.07)*</td>
<td>147.34(42.62)*</td>
<td>119.23(44.64)*</td>
<td></td>
</tr>
<tr>
<td>Sleep onset latency</td>
<td>11.8 (5.62)</td>
<td>15.92 (10.72)</td>
<td>13.75 (6.82)</td>
<td>9.78 (5.62)</td>
<td>12.87(8.17)</td>
<td>ns</td>
</tr>
<tr>
<td>Total Sleep minutes</td>
<td>485.05 (31.63)*</td>
<td>497.75 (38.61)Δ</td>
<td>497.8 (50.63)Δ</td>
<td>529.8 (48.74)Δ</td>
<td>504.98 (44.09)*</td>
<td></td>
</tr>
<tr>
<td>Sleep Efficiency</td>
<td>96.7 (1.65)</td>
<td>93.75 (3.38)</td>
<td>95.12 (2.29)</td>
<td>95.34 (2.48)</td>
<td>94.98 (2.60)</td>
<td>ns</td>
</tr>
<tr>
<td>WASO</td>
<td>2.2 (1.66)</td>
<td>2.8 (1.98)</td>
<td>2.24 (1.33)</td>
<td>2.58 (2.07)</td>
<td>2.46 (1.76)</td>
<td>ns</td>
</tr>
<tr>
<td>% Stage 1</td>
<td>4.75 (2.18)</td>
<td>4.73 (2.04)</td>
<td>4.58 (1.68)</td>
<td>6.07 (2.46)</td>
<td>5.02 (2.15)</td>
<td>ns</td>
</tr>
<tr>
<td>% Stage 2</td>
<td>46.27 (3.5)</td>
<td>44.10 (6.0)</td>
<td>43.38 (5.25)</td>
<td>42.84 (3.92)</td>
<td>43.87 (4.81)</td>
<td>ns</td>
</tr>
<tr>
<td>% Stage 3</td>
<td>4.72 (1.59)</td>
<td>5.46 (1.75)</td>
<td>5.80 (2.27)</td>
<td>5.43 (2.05)</td>
<td>5.36 (1.94)</td>
<td>ns</td>
</tr>
<tr>
<td>% Stage 4</td>
<td>20.85 (3.89)</td>
<td>22.45 (4.43)</td>
<td>22.68 (5.18)</td>
<td>23.89 (3.13)</td>
<td>22.44 (4.32)</td>
<td>ns</td>
</tr>
<tr>
<td>Total Awakenings</td>
<td>11.0 (5.8)</td>
<td>11.53 (6.38)</td>
<td>10.87 (6.21)</td>
<td>10.94 (5.2)</td>
<td>11.10 (5.82)</td>
<td>ns</td>
</tr>
<tr>
<td>Total SWS min</td>
<td>123.02 (25.0)*Δ</td>
<td>141.1 (28.63)</td>
<td>146.16 (29.72)*Δ</td>
<td>150.76 (29.29)Δ</td>
<td>140.68 (28.81)*</td>
<td></td>
</tr>
<tr>
<td>Total REM min</td>
<td>104.38 (22.89)</td>
<td>97.36 (14.09)</td>
<td>102.1 (23.47)</td>
<td>100.13 (20.25)</td>
<td>100.91 (20.21)</td>
<td>ns</td>
</tr>
<tr>
<td>No. REM sessions</td>
<td>4.68 (1.02)</td>
<td>4.60 (0.75)</td>
<td>4.55 (1.44)</td>
<td>5.42 (1.01)</td>
<td>4.75 (1.00)</td>
<td>ns</td>
</tr>
<tr>
<td>Total Leg Movements</td>
<td>18.05 (21.05)</td>
<td>19.1 (14.36)</td>
<td>37.5 (17.5)</td>
<td>15.0 (18.10)</td>
<td>22.62 (34.41)</td>
<td>ns</td>
</tr>
<tr>
<td>Movements during REM</td>
<td>7.0 (4.56)</td>
<td>7.15 (3.68)</td>
<td>8.23 (3.49)</td>
<td>10.33 (4.44)</td>
<td>8.21 (4.18)</td>
<td>ns (p&lt;.008)</td>
</tr>
<tr>
<td>Total Arousal</td>
<td>51.22 (19.33)*</td>
<td>47.90 (17.43)*</td>
<td>62.8 (15.44)*</td>
<td>68.05 (23.91)*</td>
<td>54.89 (20.38)*</td>
<td></td>
</tr>
<tr>
<td>Arousal from SWS</td>
<td>3.67 (1.71)</td>
<td>3.35 (2.13)*Δ</td>
<td>4.96 (2.54)*Δ</td>
<td>5.06 (2.65)Δ</td>
<td>4.23 (2.37)*</td>
<td></td>
</tr>
</tbody>
</table>
Tests for Group differences in serotonin and testosterone

Kruskal-Wallis test was used to compare the mean serotonin and testosterone levels among the four diagnostic groups and revealed a borderline significant effect (p=0.06). Using means adjusted for the two covariates, Age and Pubertal Level, there emerged a highly significant main effect for diagnostic group (p<.006). Interestingly, all three patient groups (TS only, TS+ADHD, ADHD only) had significantly higher levels of testosterone than controls (p<.001, p<.034 and p<.007 respectively) (Figure 3.)

Figure 3. Testosterone level group differences adjusted for Age and pubertal levels

![Testosterone level group differences adjusted for Age and pubertal levels](image)
Since serotonin levels were normally distributed, ANOVA was employed to detect differences in this variable on the second morning among the four diagnostic groups. The result of ANOVA was significant at p<.02. Specifically, the TS only group had significantly higher levels of serotonin than both the Control subjects (p=0.03) and TS+ADHD (p=0.04). Serotonin measurements across all subjects were highly significantly (p<0.001) different across the two morning samples (see Table 8).

Measurements of 5-HIAA, the primary metabolite of 5HT, were included to obtain estimates of 5HT turnover. Adjusting for Age and Pubertal Level our samples revealed highly significant main effects of 5-HIAA for diagnostic group for both first (p<.003) and second day measurements (p<.033). Concentration of 5HIAA was significantly higher in the ADHD group than all three comparison groups (ADHD>TS, p<.020; ADHD>TS+ADHD, p<.012; ADHD>Controls, p<.012). No other between group differences were statistically significant. (See Figure 4)
Neuropsychological Testing

Using ANOVA, T scores on the Tower tests (of Executive Functioning and Planning) were highly significant across groups (p=0.009), with TS only (p<0.005), TS+ADHD (p<0.023) and Controls (p<0.004) performing significantly better than the children with ADHD alone (p=0.03). However, on further analysis using contrasts controlling for age and puberty, no significant differences emerged on any neuropsychological tests between groups (NS, p<0.314).
Correlations Among Ratings of Aggressive Behaviour, Neuropsychological Tests, Neurochemical and Sleep Parameters

Correlations among the neuropsychological test T scores, testosterone and serotonin levels and the CBCL/TRF aggression subscale scores and sleep parameters for the entire sample were examined with Pearson Product-Moment correlation coefficients (the results of these analyses are presented in Table 12). Overall, based on all 80 subjects, uncorrected for age and pubertal maturity, a negative correlation between parental aggression and neuropsychological test scores suggested that the higher the Parental ratings of aggressive behaviour (CBCL) the lower the scores achieved on all three neuropsychological tests (Perseverative errors-WCST; Walk-don’t-Walk; Tower). As expected, the parental rating of aggressive behaviour was positively correlated with the Teacher rating of aggressive behaviour.
Table 12: Correlations among Ratings of Aggressive Behaviour, Neuropsychological Tests, Neurochemical and Sleep Parameters

<table>
<thead>
<tr>
<th></th>
<th>Day 2 serotonin nmol/L</th>
<th>Day 2 testosterone pg/ml</th>
<th>Day2 Percent REM sleep</th>
<th>CBCL Aggression Parent_T</th>
<th>TRF Aggression Teacher_T</th>
<th>Perseverative errors Tscore</th>
<th>Walk-dont-walk T score</th>
<th>Tower (NEPSY or Toronto) T score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 2 serotonin nmol/L</td>
<td>Pearson Correlation</td>
<td>1.000</td>
<td>.399**</td>
<td>-.273*</td>
<td>-.134</td>
<td>-.216</td>
<td>.043</td>
<td>.135</td>
</tr>
<tr>
<td></td>
<td>Sig. (2-tailed)</td>
<td>.000</td>
<td>.019</td>
<td>.246</td>
<td>.077</td>
<td>.708</td>
<td>241</td>
<td>0.025</td>
</tr>
<tr>
<td>Day 2 testosterone pg/ml</td>
<td>Pearson Correlation</td>
<td>.399**</td>
<td>1.000</td>
<td>-.136</td>
<td>-.233*</td>
<td>-.131</td>
<td>.191</td>
<td>.181</td>
</tr>
<tr>
<td></td>
<td>Sig. (2-tailed)</td>
<td>.000</td>
<td>.247</td>
<td>.041</td>
<td>.285</td>
<td>.096</td>
<td>.115</td>
<td>.000</td>
</tr>
<tr>
<td>Day2 Percent REM sleep</td>
<td>Pearson Correlation</td>
<td>-.273*</td>
<td>-.136</td>
<td>1.000</td>
<td>-.197</td>
<td>-.217</td>
<td>.042</td>
<td>.006</td>
</tr>
<tr>
<td></td>
<td>Sig. (2-tailed)</td>
<td>.019</td>
<td>.247</td>
<td>.085</td>
<td>.075</td>
<td>.718</td>
<td>.960</td>
<td>.260</td>
</tr>
<tr>
<td>CBCL Aggression Parent_T</td>
<td>Pearson Correlation</td>
<td>-.134</td>
<td>-.233*</td>
<td>-.197</td>
<td>1.000</td>
<td>.502**</td>
<td>-.330**</td>
<td>-.230</td>
</tr>
<tr>
<td></td>
<td>Sig. (2-tailed)</td>
<td>.246</td>
<td>.041</td>
<td>.085</td>
<td>.000</td>
<td>.003</td>
<td>.040</td>
<td>.004</td>
</tr>
<tr>
<td>TRF Aggression_Teacher_T</td>
<td>Pearson Correlation</td>
<td>-.216</td>
<td>-.131</td>
<td>-.217</td>
<td>.502**</td>
<td>1.000</td>
<td>-.134</td>
<td>-.216</td>
</tr>
<tr>
<td></td>
<td>Sig. (2-tailed)</td>
<td>.077</td>
<td>.285</td>
<td>.075</td>
<td>.000</td>
<td>.267</td>
<td>.070</td>
<td>.031</td>
</tr>
<tr>
<td>Perseverative errors Tscore</td>
<td>Pearson Correlation</td>
<td>.043</td>
<td>.191</td>
<td>.042</td>
<td>-.330**</td>
<td>-.134</td>
<td>1.000</td>
<td>.134</td>
</tr>
<tr>
<td></td>
<td>Sig. (2-tailed)</td>
<td>.708</td>
<td>.096</td>
<td>.718</td>
<td>.003</td>
<td>.267</td>
<td>.235</td>
<td>.001</td>
</tr>
<tr>
<td>Walk-dont-walk T score</td>
<td>Pearson Correlation</td>
<td>.135</td>
<td>.181</td>
<td>.006</td>
<td>-.230*</td>
<td>-.216</td>
<td>.134</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>Sig. (2-tailed)</td>
<td>.241</td>
<td>.115</td>
<td>.960</td>
<td>.040</td>
<td>.070</td>
<td>.235</td>
<td>.006</td>
</tr>
<tr>
<td>Tower (NEPSY or Toronto) T score</td>
<td>Pearson Correlation</td>
<td>.256*</td>
<td>.405**</td>
<td>.130</td>
<td>-.317**</td>
<td>-.256*</td>
<td>.352**</td>
<td>.304**</td>
</tr>
<tr>
<td></td>
<td>Sig. (2-tailed)</td>
<td>.025</td>
<td>.000</td>
<td>.260</td>
<td>.004</td>
<td>.031</td>
<td>.001</td>
<td>.006</td>
</tr>
</tbody>
</table>

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).
Summary of Group Differences

The following table (Table 13) provides a summary of the significant relationships that emerged between diagnostic group and the following outcome variables (percentage of REM sleep, 5HIAA levels, testosterone levels, WCST perseverative errors), selected for this study with all comparisons made to normal control subjects. Age was included as this construct has been theoretically related to each of the outcome variables of interest (Ramos Platon et al., 1990; Halperin et al., 1997; Constantino et al., 1993; Weyandt et al., 1990).

Table 13. Summary of Significant Group Differences of Aggressive Behaviour and Related Variables Comparing 3 Diagnostic Groups to Normal Controls

<table>
<thead>
<tr>
<th>Group</th>
<th>Clinical Aggression</th>
<th>% REM Sleep</th>
<th>5-HIAA levels</th>
<th>Testosterone Levels</th>
<th>WCST Perseverative Errors</th>
<th>Subject's Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>TS</td>
<td>+*</td>
<td>-</td>
<td></td>
<td>+</td>
<td>+*</td>
<td></td>
</tr>
<tr>
<td>TS+ADHD</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADHD</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+*</td>
<td>-</td>
</tr>
</tbody>
</table>

Note: This table is intended to provide an overview of the previously reported findings

+ = Significantly higher than Normal Controls
* = Approaching Statistical Significance
− = Significantly Lower than Normal Controls

(all analyses have previously been reported in the results section).
Overall, clinically aggressive behaviour was significantly more common in the TS+ADHD and ADHD group than controls, and while the TS only group [numbers??] was [F] elevated, they failed to reach statistical significance. Both TS only and ADHD groups had significantly lower percentages of REM sleep than the control group. The serotonin metabolite 5-HIAA was significantly higher in only the ADHD group compared to controls, while interestingly, all three diagnostic groups had statistically higher levels of testosterone than the comparison group. Perseverative errors on the WCST test were elevated in both the TS and ADHD groups.

Part III: Predictors of Aggressive Behaviour

Theoretical Framework: Diagnostic category versus variables related to aggression:

Hierarchical MLR analyses.

In Part I of the dissertation analysis, significant differences amongst diagnostic groups for both Parental and Teacher ratings of aggressive behaviour were revealed. Significant differences were also demonstrated among the diagnostic groups for the following variables: Day 2 Serotonin levels, Day 2 Testosterone levels, Day 2 REM latency, Day 2 REM percentage, and a trend towards a difference for WCST perseverative error t-scores. As described in detail in the introduction, previous research (in both clinical and non-clinical samples) has shown that these variables are also related to aggressive behaviour. Consequently, the relative importance of these variables in predicting aggressive behaviour in comparison to the explanatory power of diagnostic categories becomes a salient issue: are differences in aggressive behaviour inherent to the diagnostic groups, or do they reflect more fundamental differences in parameters related to aggression that vary among the diagnostic groups?
Parental Ratings of Aggressive Behaviour

The final model that emerged from the regression of the complete linear combination of predictors on parental ratings of aggressive behaviour accounted for a large and highly significant percentage of variance, $R^2 = 0.49; F(10, 58) = 5.56; p < 0.0001$.

Table 14. Hierarchical Regression Analysis Blocks in the Order of:
Age /Diagnostic Classification/Physiological & Cognitive Factors (Parental Ratings)

<table>
<thead>
<tr>
<th>Block</th>
<th>Variables</th>
<th>$R^2$</th>
<th>$R^2$ Change</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Age</td>
<td>0.16</td>
<td>0.16</td>
<td>12.57</td>
<td>0.001</td>
</tr>
<tr>
<td>2</td>
<td>Diagnostic Classification</td>
<td>0.31</td>
<td>0.15</td>
<td>4.65</td>
<td>0.005</td>
</tr>
<tr>
<td>3</td>
<td>Physiologic and Cognitive Factors</td>
<td>0.49</td>
<td>0.18</td>
<td>3.43</td>
<td>0.006</td>
</tr>
</tbody>
</table>

The first block revealed a significant contribution of age to parental ratings of aggressive behaviour, $R^2 = 0.16; F(1, 67) = 12.57; p < 0.001$. The second block of variables (the diagnostic categories) also contributed a significant amount of variance, $R^2$ change = 0.15; $F(3,64) = 4.65; p < 0.005$. However, somewhat surprisingly, the third block variables again contributed a significant additional amount of variance, $R^2$ change = 0.18; $F(6,58) = 3.43; p < 0.006$. This finding indicates that the theoretically selected aggression-related variables (physiologic and cognitive factors) contribute a significant amount of variance to
parental ratings of aggressive behaviour over and above the variance already accounted for in the model by diagnostic classification. (See Table 14)

In a second set of analyses, the order of the second and the third blocks of the hierarchical regression analysis was reversed. This enabled us to examine the independent and unique contribution of our set of physiologic and cognitive parameters related to aggressive behaviour over and above the variance in parental ratings of aggression accounted for by diagnostic category.

The first block of the analysis was identical to the initial analysis presented above, a significant contribution of subject age to parental ratings of aggressive behaviour, $R^2 = 0.16$; F (1, 67) = 12.57; $p < 0.001$. The second block of variables (physiologic and cognitive) contributed a significant additional amount of variance to parental ratings of aggressive behaviour, $R^2$ change = 0.16; F(6,61) = 2.43; $p < 0.036$. The third block of variables (the diagnostic categories) also contributed a significant amount of variance, $R^2$ change = 0.17; F(3,58) = 6.41; $p < 0.001$. (See Table 15).

Table 15. Hierarchical Regression Analysis Blocks in the Order of:
Age /Physiological & Cognitive /Diagnostic Classification (Parental Ratings)

<table>
<thead>
<tr>
<th>Block</th>
<th>Variables</th>
<th>$R^2$</th>
<th>$R^2$ Change</th>
<th>F</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Age</td>
<td>0.16</td>
<td>0.16</td>
<td>12.57</td>
<td>0.001</td>
</tr>
<tr>
<td>2</td>
<td>Physiological &amp; Cognitive Variables</td>
<td>0.32</td>
<td>0.16</td>
<td>2.43</td>
<td>0.036</td>
</tr>
<tr>
<td>3</td>
<td>Diagnostic Classification</td>
<td>0.49</td>
<td>0.17</td>
<td>6.41</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Teacher Ratings of Aggressive Behaviour

The final model that emerged from the regression of the complete linear combination of predictors on teacher ratings of aggressive behaviour accounted for a smaller percentage of variance than the analysis for parent ratings of aggressive behaviour, although the result was substantial, and statistically significant, $R^2 = 0.37; F(10, 50) = 2.89; p < 0.006$.

The first block revealed a marginal contribution of age to parental ratings of aggressive behaviour, $R^2 = 0.06; F (1, 59) = 3.57; p < 0.064$. The second block of variables (the diagnostic classification) contributed a significant amount of variance, $R^2$ change = 0.16; $F(3,56) = 3.73; p < 0.016$. The third block variables (physiological and cognitive) contributed a marginally significant amount of variance, $R^2$ change = 0.15; $F (6,50) = 1.97; p < 0.084$. (See Table 16).

Table 16. Hierarchical Regression Analysis Blocks in the Order of:

Age /Diagnostic Category/Physiological & Cognitive (Teacher Ratings)

<table>
<thead>
<tr>
<th>Block</th>
<th>Variables</th>
<th>$R^2$</th>
<th>$R^2$ Change</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Age</td>
<td>0.06</td>
<td>0.06</td>
<td>3.57</td>
<td>0.064</td>
</tr>
<tr>
<td>2</td>
<td>Diagnostic Classification</td>
<td>0.22</td>
<td>0.16</td>
<td>3.73</td>
<td>0.016</td>
</tr>
<tr>
<td>3</td>
<td>Physiologic and Cognitive Variables</td>
<td>0.37</td>
<td>0.15</td>
<td>1.97</td>
<td>0.084</td>
</tr>
</tbody>
</table>

Again, a second set of analyses was conducted in which the order of the second and the third blocks of the hierarchical regression analysis was reversed. This allowed for examination of the independent and unique contribution of the selected set of aggression
predictors (physiologic and cognitive) over and above the variance in teacher ratings of aggression accounted for by diagnostic classification.

The first block of the analysis was identical to the initial analysis presented above, revealing a marginal contribution of age to teacher ratings of aggressive behaviour, $R^2 = 0.04; F(1, 59) = 3.57; p < 0.064$. The second block variables (physiologic and cognitive factors) failed to contribute a significant additional amount of variance to teacher ratings of aggressive behaviour, $R^2$ change $= 0.15; F(6,53) = 1.70; p < 0.14$. The third block of variables (the diagnostic classification) contributed a significant amount of variance, $R^2$ change $= 0.16; F(3,50) = 4.12; p < 0.01$. (See Table 17)

Table 17. Hierarchical Regression Analysis Blocks in the Order of:
Age /Diagnostic Category/Physiological & Cognitive (Teacher Ratings)

<table>
<thead>
<tr>
<th>Block</th>
<th>Variables</th>
<th>$R^2$</th>
<th>$R^2$ Change</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Age</td>
<td>0.04</td>
<td>0.04</td>
<td>3.57</td>
<td>0.064</td>
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Path Analysis

Age was used as the primary exogenous variable in the path analysis, not only because of the age differences among the diagnostic groups, but because age (as a putative measure of the maturation process) is an important explanatory construct found in previous empirical research to be related to each of the other variables in the present investigation (e.g., aggression and sleep parameters) (Budman et al., 1998; Coble et al., 1987; Como, 1993;
For example, age was found to be inversely related to our primary measures of interest, i.e., the presence of aggressive behaviour and REM sleep variables (Ramos Platon et al., 1990; Coble et al., 1987). In the previous analyses, the effects of age on aggressive behaviour had been controlled for in order to ameliorate the effects of not having age equivalence across the groups. However, partialling out variance that can be attributed to age excludes a potentially powerful explanatory variable that may directly affect the outcome, or moderate other variables measured in the investigation.

The primary endogenous variable of interest was aggressive behaviour. In particular I used parental ratings of aggressive behaviour because this variable yielded the strongest results in the previous MLR analyses. I felt justified in examining the relationship between aggression-related variables and raw score parental ratings of aggressive behaviour instead of using residual aggression scores with diagnostic classification partialled out, because these two sets of variables accounted for independent variance in the MLR analyses. The other endogenous variables used in the path analysis were: percentage REM sleep, WCST perseverative errors, Day 2 testosterone, and Day 2 5-HIAA levels. The model I created for the path analysis specified that REM sleep, WCST perseverative errors, testosterone, and 5-HIAA all contribute to variance in parental ratings of aggressive behaviour, although age (being the more fundamental exogenous variable, a putative marker of maturational processes) contributes to variance in all of the above variables. In the model, age was also specified to have a direct effect on parental ratings of aggressive behaviour to account for all other effects of maturation on aggressive behaviour that may be mediated by variables not included in the present investigation.

The path analysis was conducted with LISREL 8.30 (Joreskog & Sorbom, 1996), using
a maximum likelihood method for estimating the overall fit function and path coefficients. The results of the analysis failed to yield a significant chi-square result ($\chi^2(6) = 6.29$, $p<0.35$), suggesting that the covariance matrix implied by the model specified did not differ significantly from the data in the observed covariance matrix (i.e., the model provided an adequate fit to the observed data). This was corroborated by an adjusted goodness of fit index of 0.95, a Root Mean Squared Error of Approximation value of 0.035, and a critical $N$ of 212.01.

Given the good overall fit of the model, I turned to examination of the path coefficients. The standardized solution for our model can be seen in Figure 5. The direct effect of age on parental ratings of aggressive behaviour did not reach statistical significance ($T = -1.7; p>0.05$). However age did have a significant effect on testosterone levels ($T = 3.54; p<.05$), WCST perseverative errors ($T=3.23; p<.05$), and Day 2 percentage REM ($T = 3.07; p<.05$), and in turn these latter two variables had a significant effect on parental ratings of aggressive behaviour, WCST ($T = -3.20; p<.05$), and Day 2 percentage REM ($T = -2.09; p<.05$). Thus, it seems that percentage REM sleep and WCST errors mediate the effect of age on parental ratings of aggressive behaviour. Consistent with these observations, when total effects were decomposed, I found that age exerted a significant indirect effect on parental ratings of aggressive behaviour ($T = -2.71; p<.05$).
Figure 5: Path analysis showing indirect effects of age on parental ratings of aggressive behaviour

-0.21 – Standardized Path coefficient (sign denotes direction of effect, red colour denotes statistical significance)

0.7 = error in equation

D2test = Day 2 Testosterone Level
pREM2 = Percentage of REM Sleep -2nd night
WCSTerr = Wisconsin Card Sorting Test Perseverative Errors
HIAA2 = 5-HIAA level 2nd morning
AGGp = Parental rating of Aggressive bx
Chapter Three

Discussion

Achieving an improved understanding of the risk of developing the outbursts of aggressive behaviour observed in 30-67% of clinical populations (Moldofsky et al., 1974; Comings et al., 1985; Freeman et al., 2000; Budman et al., 1998) of children with TS is an important challenge for researchers and clinicians alike. This thesis has contributed to the understanding of this phenomenon using both a theoretically and data-driven approach to explore the contribution of specific sleep variables, neurochemical levels, neuropsychological test performance and diagnostic classification to the expression of aggressive behaviour in children.

Predictors of Aggressive Behaviour

The primary purpose of this thesis was to identify characteristics that were unique to three different groups of children (TS, TS+ADHD and ADHD) that would indicate increased risk of manifesting aggressive behaviour. Although diagnostic category proved to be a significant risk factor for aggressivity, interestingly, there emerged other equally important factors common to all three groups of children, exclusive of, and in addition to diagnosis, that offered unique and independent contributions to the risk of demonstrating aggressive behaviour.

Prior research has established links between aggressive behaviour and the following variables: measures of response inhibition (Coccaro, Kavoussi, Cooper, & Hauger, 1997b), hormone and neurotransmitter levels (Bernhardt, 1997), and REM sleep parameters (Morden et al., 1968). It was interesting to explore the extent to which these factors...
contribute to aggressive behaviour, independent of diagnostic classification. Diagnostic classification of psychopathology is a way of grouping together individuals on the basis of overt behavioural signs and symptoms, without respect to underlying pathophysiological processes. However, in the present investigation, a linear combination of aggression-related variables accounted for a significant amount of variance in parental ratings of aggressive behaviour, and even after diagnostic classification had been accounted for in the regression model. This finding is consistent with a 'spectrum' notion of psychopathology in which differences among diagnostic groups in criterion behaviour are better explained by including variables that may serve as putative markers of underlying pathophysiological processes (e.g., percentage of REM sleep, REM latency, testosterone and 5-HIAA levels). This spectrum formulation is also consistent with the high prevalence of comorbid psychiatric diagnoses (particularly ADHD and Obsessive-Compulsive Disorder) in children with TS and other psychiatric disorders. Data-driven exploratory stepwise regression analyses corroborated these results by revealing 5-HIAA levels and response inhibition (WCST) to be significant independent inverse predictors of aggressive behaviour (parental ratings), in addition to ADHD and TS+ADHD diagnostic classifications.

If, in the future, it becomes possible to measure all the relevant variables reflecting underlying pathophysiological processes, then one could expect that diagnostic classification would no longer account for a significant amount of variance in the ratings of aggressive behaviour.

Children with TS were rated as significantly more aggressive than control children only when they also met diagnostic criteria for ADHD. This finding supports the notion of heterogeneity within the population of children with TS, and the importance of considering comorbid psychiatric diagnoses. It was encouraging to observe that this result
revealed the existence of a group of children with TS who do not manifest clinically significant levels of aggressive behaviour, which provides additional evidence that children with TS and comorbid ADHD more closely resemble those with a diagnosis of ADHD on levels of aggressive behaviour, while behaviorally, children with TS-only were more similar to controls.

The findings show that although diagnostic category is a significant predictor of increased risk of aggressive behaviour, there are other factors that explain additional variance in the overall model. The success of this approach suggests that future research on the determinants of predicting aggressive behaviour in children should take a broader perspective beyond the overt classification of diagnostic category. Based on the strong design of the current study, which included stringent assessment for comorbidity, drug-free subjects and the use of pathological and normal control comparison groups all undergoing the same rigorous study protocol, I have provided an empirical demonstration of the contribution of comorbid ADHD to the diagnosis of TS (on sleep parameters, neurochemical levels and behavioural measures) by revealing the similarities of these two diagnostic classifications, the results of comorbidity, and acknowledging the characteristics unique to each independent diagnosis.

**Role of REM Sleep in Aggressive Behaviour**

Results of the hierarchical regression analysis performed in this thesis support our hypothesis that children with TS, TS+ADHD and ADHD differ beyond what is described in the categorical diagnostic determinants and that these features are predictive of aggressive behaviour. Our objective results suggest significant physiological differences e.g., REM sleep parameters and neurochemical levels, that each explain unique and independent contributions to the variance in our outcome variable of parental ratings of aggressive
behaviour in addition to, and exclusive of, the overt characteristics understood by diagnostic criteria.

This suggests that the secondary variables examined were important determinants of aggressive behaviour, and should be considered an integral part of a comprehensive clinical assessment. In addition, because of the developmental course frequently observed in children with TS, such as the pre-existence of attention problems, or ADHD prior to the onset of motor and vocal tics, our findings assist in the understanding that although the clinical diagnosis may change over time (with the advent of new symptomatology), the underlying pathology and/or dysregulation of neurochemicals may be a better indicator of the risks of developing aggressive behaviour than the present existing clinical diagnosis.

The Impact of Maturation on Aggressive Behaviour Factors

Overall, a significant result was the impact that age had on almost all the variables examined in this study; supporting previous theoretical research that age is a putative marker of maturational processes. This was strongly observed in our path analysis where increased age was a significant predictor of higher testosterone levels, increased percentage of REM sleep and an improved ability to inhibit responses (WCST perseverative errors). Furthermore, given that our analyses revealed that since low percentages of REM sleep and compromised scores on tests of response inhibition were significant predictors of increased parental aggression ratings, it can be suggested that the children exhibiting clinically significant levels of aggressive behaviour, outside the normal range for their chronological age cohort, may in fact be demonstrating a maturational delay irrespective of their clinical diagnosis of TS or ADHD. It has been previously reported that aggressive and maladaptive behaviour in children may be related to maturational factors (Halperin et al., 1997) affecting
5-HT levels in ADHD, although there was no control or comparison group data available. I have now supported this hypothesis and added new information using our four-group sample design. This study revealed the significant impact of maturation not only on serotonin levels, but also clearly indicated the effects of age and pubertal levels of maturation on additional theoretically and data-driven aggression-related variables.

Sleep Variable Results

The results of this thesis support the first hypothesis that there would be a significant difference in the percentage of REM sleep between the four groups of subjects. While the Tourette’s Syndrome only group (TS) and the ADHD group each had significantly less total REM sleep time than controls, it was surprising that the group with both TS and ADHD was not statistically different from controls (Figure 1). This finding suggests the presence of a moderating effect when the two disorders are combined, protecting from the manifestation of the REM sleep deficiency that is observed when either diagnosis occurs independently.

Although the percentage of REM sleep was similar in both groups with TS, there was a slight, yet not significant increase in the comorbid TS+ADHD group mean. These results confirm and extend previous studies based on parental reports and polysomnographic studies describing the intrinsic sleep problems characteristic of children with ADHD. In this study it was determined that percentage of REM sleep was one of the objective sleep parameters which was reduced in the ADHD population, and only modestly compromised in the comorbid TS+ADHD group of children.
An explanation for the possible protective interaction of the comorbid diagnoses of TS and ADHD on the percentage of REM sleep is more complicated. Comparison with data from previous polysomnographic sleep studies is difficult because most of the researchers have not provided essential information about the methodology, nor have they allowed the subjects to awake ad lib (Voderholzer et al., 1997; Moeller et al., 1992; Mendelson et al., 1980). This practice may have compromised the REM sleep measurement given the knowledge that normal circadian regulation of REM sleep accounts for a propensity of more REM sleep in the latter part of the sleep cycle (Borbely, 1982). It may be interesting in a future study to reanalyze our own sleep data with a predetermined morning cutoff time imposed, to observe whether differences in overall sleep parameter results would be significant.

One hypothesis for the differences in percentage of REM sleep between the groups could be derived from neurochemical research in TS and ADHD. Treatment success in the ADHD population with stimulant medications, including methylphenidate and dextroamphetamine (Cohen et al., 1992b; Zanetkin et al., 1985) is believed to be a result of manipulation of multiple neurotransmitter systems which primarily release neuronal DA and norepinephrine (NA), block DA and NA reuptake and inhibit monoamine oxidase metabolism of DA (Shenker, 1992). Similarly in TS, the majority of neurochemical evidence implicates the catecholamines, including dopaminergic and noradrenergic systems (Singer et al., 1991), with the majority of evidence supporting a dopaminergic dysfunction (Brett et al., 1995). Therefore, although both ADHD and TS appear to involve an imbalance of catecholamines, findings suggest that each disorder has its own specific biochemical dysfunction, with elevated levels of dopamine observed in TS and compromised levels of
dopamine in ADHD (Sheppard et al., 1999). Provided that the neurotransmitter systems implicated in ADHD and TS are intimately related, it can be posited that a dysfunction in one catecholaminergic system may cause an imbalance in another (Sheppard et al., 1999) or the additive effect of the two separate disorders may assist in balancing the catecholaminergic system in certain neuroanatomical circuits.

The importance of catecholamine pathways for the maintenance of arousal and REM sleep (Fuxe & Lidbrink, 1973) and serotonin pathways for the induction of REM sleep has been well established (Horne, 2000), and it is further understood that an imbalance in these systems could result in disrupted sleep architecture. Our observation that the pure TS group and ADHD subjects demonstrated significant reductions in percentages of REM sleep is consistent with this view.

Our results challenge reports of reduced percentage of REM sleep in patients with only TS (Glaze et al., 1983), although this may be accounted for by methodological differences. Validity of previous studies was frequently compromised by medication usage among the subjects during the time of sleep recordings and the failure of most authors to address issues of comorbidity (Jankovic et al., 1987; Drake et al., 1992). Also, it is often unclear whether the subjects awakened naturally or were awakened; the latter circumstance may have directly compromised late morning REM sleep episodes (Borbely, 1982).

Our results are consistent with a recent review of sleep disturbances in children with ADHD (Corkum et al., 1998; Nahas et al., 1977). Sleep disruption in children with ADHD has been frequently documented (Trommer et al., 1988; Kaplan et al., 1987; Giannotti et al., 1997), although most reports have been based on subjective data gathered from clinical
observation and parent reports. Also, according to Ball (1995) the primary criticism of sleep research in children with ADHD has been the limited number of polysomnographic studies (a total of 100 child subjects up to 1995) that have been conducted. The earlier study results were confounded by failure to control for medication use, differences in methodology, number of sleep nights recorded and few subjects per study (Busby et al., 1981), making the reliability questionable and often making replication of any of the findings impossible (Greenhill et al., 1983).

In the second hypothesis of this thesis it was posited that significant differences in REM latency times would be evident between two of the four groups of children. Indeed it was found that ADHD children took significantly longer to initiate their first REM period than children with TS+ADHD. Notably, controls, TS and TS+ADHD did not differ significantly in this regard. Two other polysomnographic studies have reported a longer latency to the first REM period in ADHD children (Busby et al., 1981; Haig et al., 1974) though not all subjects included in these studies were medication free. Ramos Platon et al. (1990) reported greater REM latency in 6-9 year olds with ADHD compared to controls, but not in the 10-11 year old group of children with ADHD. Unfortunately, there were only a total of 10 children in the first age group and 3 included in the latter, making such differentiation difficult to generalize to a larger population.

In our own results, the absence of a significant difference in percentage of REM and REM latency between the TS+ADHD groups vs. Controls, while observing a significant difference on the same variables between Controls and both TS and ADHD groups, again supports a possible modulating affect when the two disorders are combined. Indeed it appears that when TS is present together with ADHD the probability of finding REM
abnormalities is reduced. An alternative hypothesis is that although phenomenologically similar, the ADHD syndrome in association with TS has different etiologic mechanisms than "pure" ADHD or "pure" TS.

This result supports the hypothesis proposed by Miller and Kraft (1992) that there may be a relationship between sleep problems in children with ADHD and the presence of daytime behavioural difficulties. However, it is important to note that the finding does not generalize to the groups of aggressive children with TS + ADHD, or normal controls. It can be suggested from this observation that children with ADHD, or TS alone, have different neurochemical profiles from children with TS + ADHD, which may be protecting them from suffering from the detrimental effects of low levels of REM sleep. For example, serotonin may play a role given that it has been shown to contribute to the onset of REM sleep, and to be related to sleep regulation in children, adults and animals (Cohrs et al., 2001; Jouvet, 1968; Adrien, 1995).

Furthermore, although the children with ADHD spent the longest time sleeping, in this study this group demonstrated significantly compromised percentage of REM and REM latency. It is important to recall that the children in this study were permitted to fall asleep and awaken ad lib, in an attempt to obtain the most accurate measurement of actual sleep time. Previous studies have often followed specific morning wakening times for the subjects, artificially determining the natural sleep and arousal times. Our method has allowed us the opportunity to observe the contribution of REM sleep to the entire night's sleep without such interference. REM sleep has been reported as an important physiological phenomenon whereas deprivation may cause disturbances in the processes leading to normal physiology and behaviour and generalized increase in neuronal excitability (Gulyani et al.,

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and symptoms of fibromyalgia (Moldofsky & Scarisbrick, 1976). Although the exact purpose for REM sleep is yet unknown, it has also been hypothesized by Roffwarg and Dement (Roffwarg et al., 1966) that REM sleep may contribute to overall brain maturation and the maintenance of the proper functioning of the aminergic and cholinergic systems that regulate sleep (Mallick & Joseph, 1997). Our results of increased aggressive behaviour and compromised REM sleep in the ADHD group data seem consistent with these hypotheses and provide further evidence that children with ADHD may suffer from a dysregulation of arousal (Barkley, 1990; Busby et al., 1981), and that the REM sleep deprivation may be exacerbating problems with impulsivity and behavioural control.

The third hypothesis investigated whether children with clinically significant levels of aggressive behaviour compared to non-aggressive children across all the diagnostic groups would manifest lower percentages of REM sleep. Results from this study do not differentiate clinically aggressive children from children with sub clinical levels of aggression, or non-aggressive children on the basis of REM sleep parameters. This supports differences observed in sleep architecture found to be related to diagnostic group, as discussed in the second hypothesis. Notably, because stringent criteria for stratifying the groups into clinical and non-clinical levels of aggressive behaviour reduced the number of subjects included in the analyses substantially, this question can not be answered definitively until larger numbers of subjects per group become available. Also, the method employed may have excluded children who were within the borderline clinical range for aggressive behaviour, who may have met criteria for clinically aggressive on alternate measures.

Finally, the sleep study results strongly supported the need to incorporate into the design a minimum of two nights in the sleep lab in order to accurately interpret the results.

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The sample as a whole demonstrated highly significant acclimatization effects from the first to the second night, with marked improvement noted on the majority of sleep parameters during the second night's recording.

**Neurochemical differences Between Groups**

*Testosterone:*

Interestingly, after correction for age and level of pubertal maturity, all three diagnostic groups had significantly higher levels of testosterone than controls. Most intriguing, after correction for age, the children with ADHD had the highest levels of testosterone of all groups. There were no statistical differences on testosterone measurements between the three diagnostic groups (TS, TS+ADHD and ADHD), although there was a trend noted for the TS+ADHD group to have lower testosterone measurements than either the TS or ADHD groups.

It was very interesting that when the ADHD group was compared to the other three groups, without correction for age, there were no significant differences observed in testosterone levels. This was exceptionally perplexing since the mean age of the ADHD children was significantly lower than all three comparison groups (controls were the oldest subjects, followed by TS, TS+ADHD, and ADHD the youngest). Therefore, the youngest group of children in this study had the highest levels of testosterone. This observation is all the more intriguing since the ADHD group rated significantly lower than all three comparison groups on the Pubertal Maturity rating scale.

Therefore, with respect to the **fourth hypothesis** of this thesis, the subjects with the highest age-adjusted testosterone levels manifested the highest levels of aggressive behaviour as reported by parents and teachers. Given that all three diagnostic groups had significantly
higher testosterone levels than Controls, their high testosterone levels (once corrected for age), combined with their significantly higher levels of aggressive behaviour (ADHD group), add support to the body of research that suggests high testosterone levels are related to increased irritability (Harris, 1999), low levels of frustration tolerance (Gray et al., 1991), impulsivity (Gladue, 1991), and an increased risk of disruptive behaviour (Kirkpatrick et al., 1993). The results of the path analysis in this study strongly suggest that the unusually high levels of testosterone for age and level of pubertal maturity, as observed in the ADHD group of children, may be contributing to their aggressive behaviour reported by both parents and teachers.

Consistency between testosterone from day one to day two provided support for the reliability and the sensitivity of the methodology selected for this study.

**Serotonin:**
Measures of serotonin metabolism were equally interesting. Concentration of 5HIAA was measured in overnight urine collection. According to the fifth hypothesis, the more aggressive and more hyperactive subjects in this study should have the lowest levels of serotonin among all the subjects. It was very interesting to find that the ADHD group levels were significantly higher both mornings (predicted values corrected for age and pubertal maturity) compared to all three other groups. No other significant group differences were observed. This result supports lines of evidence that have indicated abnormal serotonergic function in children with disruptive behavioural disorders, e.g., ADHD, Oppositional-Defiant Disorder (ODD) and Conduct Disorder (CD), all of whom demonstrate significant problems with hyperactivity, impulsivity and aggression. Although some reports have associated low central 5HT function in children with disruptive behaviour disorders (Krueger et al., 1990), others have reported higher 5HT function (Halperin et al., 1997) by measuring
either CSF levels of 5-HIAA (Castellanos et al., 1994) or responses to pharmacological challenge tests (Coccaro et al., 1997b). This observation also provides additional evidence for the argument that children with ADHD are dissimilar to the children with TS+ADHD, as indicated by the findings of this study, i.e., REM sleep parameters and salivary testosterone concentration.

With the understanding that there is a considerable amount of interaction between the dopaminergic and serotonergic systems (Kelland and Chiodo, 1996), it is not surprising that ADHD (for which the “dopamine hypothesis” currently challenges excess or deficiency of dopamine in ADHD) (Shaywitz et al., 1994) is so commonly diagnosed within the TS population. However, the specifics of the relationship between DA and ADHD remain unclear. Although a number of studies have investigated the neurochemical indicators of DA functioning in ADHD (Rogeness et al., 1992; Zametkin, Nordahl, & Gross, 1990), there have been no particularly robust findings. There is also a paucity of well-controlled neurochemical studies comparing TS-only with and without comorbid ADHD, the results of which may provide important insight into disentangling the complex dissection between the two sets of symptoms. Where the scientific challenge lies is in developing a clear understanding of how these two separate disorders with contradicting neurochemical diathesis, when comorbid, undergo changes that mediate and moderate some of the excessive behaviours and sleep parameters exclusive to each disorder. It would have been interesting in the current study to include a 24-hour urine collection as a simple and non-pharmacological manipulation of the subject’s system, to estimate the regional rates of 5HT turnover. Reliability studies have shown a significant correlation between 5-HIAA levels collected during 2 consecutive 24-hour periods of r=0.82, p<0.0001, and it has been
suggested that this method of measurement may be a non-invasive procedure to consider for identifying depressed and other psychiatric patents (Garvey, Noyes, Woodman, & Cook, 1994). This method of collection would have provided the opportunity to measure the ratio of 5-HIAA to 5HT and provide and estimate of the biochemical index of synaptic activity. The design of the current study prohibited monitoring urine collection for the necessary time (24 hrs) required for serotonin turnover analysis; however future studies may wish to consider incorporating this procedure into their design.

**Study Limitations and Areas for Future Research**

There are a number of limitations to the current study. First, there may have been a sampling bias due to the fact that the children with TS and TS+ADHD were recruited from a specialty TS clinic. These children may represent the more severe end of the spectrum of this disorder because milder cases of TS may go undiagnosed, and/or are often managed by family physicians and paediatricians, and may not seek treatment at a specialty clinic. However, there was a range of tic severity within the two TS groups, and many of the children were not seeking pharmacological interventions, which suggests there were varying degrees of the disorder within the samples. I would suggest including a wider recruitment of children with TS, particularly from primary health care professionals, to better understand the similarities and differences in the range of severity of TS and the underlying physiological factors.

Secondly, the ADHD group was significantly younger than the other three groups. Although age and pubertal maturity were included as covariates in the statistical analysis in an attempt to control for these, there may be differences present in older children with ADHD that I was unable to observe compared to our sample. Also, because TS is a
disorder that changes over time, with motor and vocal tics appearing in a waxing and waning pattern, and an unpredictable onset of attentional problems or obsessive compulsive behaviour, it would not be prudent to suggest that the results of this study are generalizable to all children with TS at all ages during the entire course of their development. This is especially so because of the observation that the majority of TS cases experience an overall and sustained reduction in tics as they emerge from their teens (Leckman et al., 1998). It would be very interesting in future studies to repeat this study with the same children to have the opportunity to directly observe the impact of development and maturation on objective variables, e.g., the sleep parameters and neurochemical levels, as well as skill development in the area of executive functioning and the increase or decrease of aggressive behaviour. A parallel study inviting the participating parents of the children (particularly the parent(s) who have a common diagnosis) would be of great interest to investigate whether the sleep parameters and other objective indicators of aggressive behaviour indicated a heritable component.

Third, groups of children with comorbid obsessive-compulsive disorders (OCD) were intentionally excluded (i.e., TS with comorbid OCD, and TS+ADHD plus OCD) from this phase of the study due to time and financial restraints. However, understanding that OCD is present in 50% of the clinical population of TS, and OCD is thought to be a disorder of dysregulation of 5HT, these are important populations to consider for comparisons in future studies.

Fourth, TS and the majority of childhood behaviour is interactively affected by a host of influences. While there is mounting evidence to support neurobiological cause, stress within the family, from peers or within the school setting has been shown to increase
the frequency and intensity of vocal and motor tics. Although adults with a single diagnosis of TS report no impairment of self-concept or increased social anxiety, adults with TS and comorbid OCD indicate significantly higher levels of anxiety and lower self-concept than healthy controls (Thibert, Day, & Sandor, 1995). Conversely, it is far more common for children with ADHD to be rated as significantly more aggressive, louder, more annoying and more impulsive by their peers than it is for children with TS (Barkley, 1991; Costello et al., 1996). However, given the disruption to social development, the impairment in adaptive functioning resulting from impulsive behaviour, and the high comorbidity of ADHD and TS, more studies are needed to better understand the differential impact of the various comorbid conditions on peer relations and family relationships in children with TS.

Finally, as many of the children involved in this study later sought pharmacological treatments for their motor and/or vocal tics or attentional problems, a follow-up investigation repeating the polysomnographic sleep study may provide insight into the affects of various medications on the specific sleep parameters of these children. It is a great advantage to have controlled, drug-free baseline data from the children who participated in this study, which could be quantitatively compared to active-treatment data. The observation of improvement or decline in sleep parameter quality could provide insight into future treatment decisions.

Summary

The objective of this thesis was to investigate the relative contribution of REM sleep, serotonin levels, testosterone levels, and executive function to daytime aggressive behaviour in children with Tourette’s Syndrome and associated disorders. This study revealed that
aggressive behaviour was clearly associated with diagnoses of TS + ADHD and/or a diagnosis of ADHD alone, though less frequent in children with TS only compared to normal controls. This supports the understanding that children with TS only are more similar to controls than the comorbid group on the level of aggressive behaviour they exhibit. ADHD children were rated as more aggressive than any other comparison group in this study. All three diagnostic groups had higher levels of testosterone compared to controls, and although the ADHD children were the youngest subjects, their testosterone levels were the highest of all four groups. In addition, the ADHD children had higher 5HIAA levels than all other comparisons. Dysregulation of neurochemical systems has been suggested as an indicator of delayed maturation in children with ADHD. There were deficits in percentages of REM sleep in the TS and the ADHD groups, although the comorbid group (TS+ADHD) manifested normal sleep parameters. I suggest the combination of TS and ADHD produces a moderating neurochemical response that appears to improve the physiology required to attain normal sleep patterns.

The understanding of the differences between children with TS only, TS with comorbid ADHD and ADHD only, has expanded as a result of this study, and provided further evidence to support the distinction between these three groups of children. This study has added support to TS being a “model developmental neuropsychiatric disorder” (Cohen and Leckman, 1994) by demonstrating the benefit of combining basic biopsychological research with clinical considerations by exploring the important relationship between internalized biology and externalized behaviour. In future studies and in clinical practice the three clinical groups should be considered separate and unique rather than the assumption that the diagnosis of TS+ADHD is simply a combination of the
symptomatology of the two disorders.
Reference List


Cetin, M., Cilden, S., & Burkovik, Y. Biochemical and neuroendocrinergic indicators of aggressive behavior: A controlled study. European Neuropsychopharmacology 6 [Supplement 4], S1-158. 1996. Abstract.


amines in obsessive compulsive disorder, Tourette's syndrome, and healthy controls.

Neuropsychopharmacology, 12, 73-86.


[Abstract]


APPENDICES
Dear Dr. Sandor and Ms. Stephens:

Re: Your research protocol entitled, "REM Sleep and Neuropsychological Patterns in Children with Tourette Syndrome"

We are writing to advise you that the Student Education Ethics Review Committee (Human Research) has granted approval to the above-named research study.

The approved revised consent form is attached. Subjects should receive a copy of their consent form.

During the course of the research, any significant deviations from the approved protocol (that is, any deviation which would lead to an increase in risk or a decrease in benefit to human subjects) and/or any unanticipated developments within the research should be brought to the attention of the Office of Research Services.

Best wishes for the successful completion of your project.

Yours sincerely,

Tom Fleming
Ethics Review Officer

TF/pp

Enclosure 164

cc: Dr. U. Shafir, Ms. M. Cascone
UHN #99-H029

Ms. Robyn Stephens
mp 10-329
Department of Psychiatry
University Health Network

Dear Ms. Stephens:

The protocol entitled "REM Sleep and Neuropsychological Patterns in Children with Tourette's Syndrome" and the revised consent form (dated July 15/99) have been reviewed by the University Health Network Research Ethics Board. The proposal is approved from an ethical standpoint for the next 12 months.

If, during the course of the research, there are any serious adverse events, substantial changes in the approved protocol or any new information or developments which must be considered with respect to the study, these should be brought to the attention of the Board.

Yours sincerely,

[Signature]

Ronald Heslegrave, Ph.D.
Chair, University Health Network Research Ethics Board

RH/bh

Sept. 15/99

Date of Approval

Sept. 15/2000

Expiry Date of Protocol
September 11, 2000

Ms. Robyn Stephens
mp 10-329
TWD

Dear Ms. Stephens:

RE: 99-H029 REM Sleep and Neuropsychological Patterns in Children with Tourette’s Syndrome

I am pleased to inform you that the above mentioned research protocol has received continued approval for the next 12 months from the University Health Network Research Ethics Board.

Best wishes for the successful completion of your project.

Yours sincerely,

Ronald Heslegrave, Ph.D.
Chair, University Health Network Research Ethics Board

RH/mm

15 September, 1999
Original Date of Approval

16 September, 2001
Expiry Date of Protocol
REM SLEEP STUDY

ASSENT FORM
for children and youths aged 6-16

Robyn Stephens, a PhD Student, Fellow, Department of Psychiatry, and Dr. P. Sandor from the Tourette's Syndrome Clinic at the Toronto Western Hospital are trying to learn more about Tourette's Syndrome in children and young adults. They want to find out what makes children with these problems get angry, and sometimes lose their tempers.

I understand that I will spend two (2) nights sleeping over at the Toronto Western Hospital. My mom/dad and I will go the sleep lab at the hospital at 8:30 on a Friday night. Before I fall asleep the sleep lab technicians will place wires on my scalp and skin with sticky tape. These wires make it possible to study my sleep patterns. One of my parents/guardians will sleep over with me. In the mornings I will spit into a cup to give Dr. Sandor and Robyn Stephens a sample of my saliva. I will also give them a sample of my urine first thing in the morning. If I need help getting the sample my mom or dad will help me.

After that I will fill out forms about my behaviour with my parents/guardian, and do some activities for about one (1) hour that will test my ability to organize things and to plan ahead. My parents and my teacher(s) will also fill out forms for Robyn Stephens and Dr. Paul Sandor about my behaviour at home and in the classroom. During the day my mom/dad and I will leave the hospital and come back at 8:30 Saturday night for one more night in the sleep lab. We will leave the hospital Sunday morning at about 8:30 am.

This study will not help me. I will not have any pain and I will be in no danger during the study.

I understand that, I don’t have to do this, and even if I decide not to take part, I will get the best available help with my problems at the Toronto Western Hospital. I know that I can change my mind at any time and say that I don’t want to be in this study, even if my parents/guardian say it’s okay for me to be in it. I understand that information about me will be stored in a locked cabinet, in a locked room and will not have my name on it. Five years after the study is finished all the information about me will be
destroyed. My privacy will always be protected. My name will not be used if the results are published.

I understand that if I tell Robyn Stephens or Dr. Sandor that I am being hurt either physically or emotionally by my parents, teachers, doctors or anyone else, they must report this to someone who will check to make sure I am okay.

It is also possible that a judge could order Robyn Stephens or Dr. Sandor to reveal what I have said to them or the results of my tests.

I have talked to Robyn Stephens or Dr. P. Sandor about this study and they have answered all my questions. I want to come to the interview, to do some testing, and to stay over for two nights in the sleep lab. I have been given a copy of this consent form.

_________________________  _________________________
Signature                  Printed Name

_________________________
Witness                    Date
REM SLEEP AND AGGRESSIVE BEHAVIOUR IN CHILDREN WITH TOURETTE'S SYNDROME (TS), ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) AND COMORBID TS AND ADHD

PARENT/ GUARDIAN
CONSENT FORM

Purpose:
The purpose of this study is to gain a better understanding of children with Tourette's Syndrome, and how the quality of their sleep may affect their daytime levels of aggressive behaviour. We will also be measuring testosterone (a male hormone) in saliva and the neurotransmitter serotonin (in urine samples). Testosterone and serotonin have been reported to have effects on sleep and aggressive behaviour in other studies. Finally, we will be looking at the children's ability to plan ahead, their organizational skills and their ability to control impulsive behaviour. This study will involve four groups of children, those 1) with Tourette's Syndrome, 2) with Tourette's Syndrome and Attention Deficit Hyperactivity disorder (ADHD) 3) with ADHD alone and 4) healthy controls. The information we gain from this study may help us to have a better understanding of the different factors that increase the risk of children with Tourette's Syndrome developing aggressive behaviour.

Sleep Study:
My child will take part in a two-night sleep study in the sleep lab at the Toronto Western Hospital. I will arrive at the Sleep Lab on the 7th Floor of the Main Pavilion of the Toronto Western Hospital at approximately 8:30 pm on the Friday night I have arranged with Robyn Stephens. During the evening, my child will have several thin wires placed on his/her scalp and skin, which will record EEG waves. This will enable the technicians to obtain the data that will describe the architecture of my child's sleep. I may sleep in a second bed in the same room as my child in the sleep lab during the evenings.

Appendix 5 – Parental Consent Form
Saliva and Urine Samples:

On the following two mornings between 7:00 and 9:00 am (following the sleep studies), my child will be asked to provide a saliva sample (2-3 ml) by spitting into a cup. Secondly, my child will be asked to provide a first morning specimen of urine. They will be asked to void, with my assistance if necessary, their morning volume of urine into a clean, dry container. We will be given instructions as to how to cleanse the external genitalia before voiding. A complimentary breakfast for both my child and me will be delivered to the sleep lab.

Questionnaires

From approximately 9:00 am to 9:30 am on the Saturday morning, I will participate in an interview with Robyn Stephens that will also take approximately thirty minutes. I will be asked questions about my child’s past and present health. I will then be asked to fill out several questionnaires regarding my child’s behaviour at home, and one questionnaire about my own behaviour. While I am filling out these questionnaires, my child will participate in approximately one hour of neuropsychological testing with Robyn Stephens. These tests are non-invasive, and include tests of general intelligence, organizational skills, ability to plan ahead and fine motor skills.

I will also be responsible for taking home four short questionnaires for my child’s teacher(s) to fill out about my child’s behaviour in the classroom. The teacher’s will be provided with a stamped, addressed envelope to return the completed questionnaires to the TS clinic.

At approximately 11:00 am, I may leave the hospital with my child. A light lunch will be provided for my child and me in the sleep lab if we wish to stay in the hospital during lunchtime (approximately 12:00 – 1:00 pm). We will return Saturday evening at approximately 8:30 pm for the second night of the sleep study. If we return to the sleep lab between 5:00 and 6:00 pm. on Saturday night, complimentary dinners will be available for my child and me. On Sunday morning, after my child has provided the second urine and saliva samples, we are free to leave the hospital, as our participation in the study will be complete. Complimentary breakfast for my child and me will be available in the sleep lab Sunday morning.

Risks and Benefits:
There will be no direct benefits to my child or me from this study. The possible risks to my child, or me could be (1) an emotional upset evoked by talking about sensitive issues, and (2) feeling uncomfortable sleeping in unfamiliar surroundings.

I understand that if I refuse to participate in this study, my child will continue to receive the best available treatment at the TS clinic and The Toronto Western Hospital as usual. My child will be asked separately for his/her assent to participate in this study, and he/she will have the right to refuse any involvement.

I understand that research records containing personal information about my child can be subpoenaed by the Courts for legal purposes.

I am aware that should the researcher suspect or have information disclosed to them about possible child abuse or neglect, they are required to report that information to the appropriate children's authorities.

I have been assured that strict confidentiality of the data will be maintained at all times. My child's file and personal data will be coded with a number and referred to by number only. Their name will only appear on a single Master List, which will be kept by the Principal Investigator in a locked cabinet in a locked office. All data collected will be kept in a locked cabinet in a locked office. Results of this study may be published and/or presented at a conference, however no names will be associated with the data. All raw data will be disposed of five (5) years after completion of this study by shredding files or erasing computer disks.

I, ___________________________, have read and understand the consent form for this study. I have had the purposes, procedures, and technical language of this study explained to me by Robyn Stephens. I have been given sufficient time to consider the above information and to seek advice. I have received a copy of this consent form for my information. If I have further questions or problems regarding this study I will contact Robyn Stephens, PhD Student, OISE/University of Toronto, Principal Investigator at (416) 630-5800, ext. 2149. I understand that this study is part of Robyn Stephens’ PhD thesis.

I may also call Dr. R. Heslegrave, Chair of the University Health Network Research Ethics Board at (416) 340-4557, who will answer questions about my rights as a subject in a research study.
I confirm that my child is not at present participating in any other research study.

Upon completion of my child's sleep study I will receive a cash payment of sixty ($60.00) as reimbursement for travel and parking expenses.

By signing this consent form, I am indicating that I agree to participate in this study with my child ________________________________.

Dated at The Toronto Western Hospital this ______day of ________19/20______.

_________________________ _____________________________
Patient's Name (please print) Patient's Signature

_________________________ _____________________________
Name of Parent/Guardian Parent/Guardian Signature

_________________________
Witness
Name of Person Professional Relationship Signature
Obtaining Consent

For further information, contact:
Robyn J. Stephens, Principal Investigator
Tourette's Syndrome Clinic
Toronto Hospital (416) 603-5800 x2 149

Appendix 6- Teacher Information Letter
Dear Teacher:

We are asking your cooperation in a research study which is being conducted by Robyn J. Stephens and Dr. Paul Sandor of the Tourette's Syndrome Clinic at the Toronto Western Hospital. A child in your class is voluntarily participating in this study, and we are asking for your involvement in reporting how he or she has been behaving in your classroom. We realize this request is only one of many demands on your time, however we have found that in behavioural research involving children, it is vital to include teachers' observations, as time spent in the classroom represents a major component of the child's active day.

His/her parent(s) are providing you with one set of four (4) different behavioural questionnaires. We ask if you could please complete these forms, and return the package to the researchers in the enclosed postage paid envelope at your earliest convenience. We request that you indicate on these questionnaires how this child has behaved in your class during the previous few weeks.

We thank you again for your time and your valued contribution to this study. Should you have any questions regarding the questionnaires or the study, please feel free to contact Ms. Robyn J. Stephens, Tourette's Syndrome Clinic, Toronto Western Hospital (416) 603-5800 ext. 2149.

Best Regards,

Robyn J. Stephens, MA
Fellow, Department of Psychiatry
University Hospital Network~Toronto Western
PhD Candidate / University of Toronto
Endnotes

The tics severity rating was measured using the following anchor points:

"0" = No tics

"1" = Mild: Motor and/or vocal tics of the intensity that is similar to normal movement, and do not attract unwanted attention.

"2" = Moderate: Motor and/or vocal tics that are clearly more pronounced than normal movements, and which attract unwanted attention.

"3" = Severe: Motor and/or vocal tics that markedly and frequently interfere with function or cause physical discomfort.

The information regarding the severity and frequency of aggressive behaviour and tics severity was extracted and rated on a four point clinical global impression scale by an experienced assessor, using the following anchor points:

"0" = No aggressive behaviour present.

"1" = Verbal aggression (yelling, screaming), more than three times per week and/or physical violence towards inanimate objects without property damage. Door slamming, throwing objects more than three times per week or physical damage less than one time per week.

"2" = Verbal aggression and physical violence towards inanimate objects leading to property damage (punching or kicking holes in walls, broken doors or windows), more than once a week, or physical violence towards people less than one time per week.

"3" = Verbal and physical violence towards people (pushing, hitting, kicking) more than once per week. Physical violence towards animals more than once per week.