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Clinical and Attentional Effects of Acute Nicotine Treatment
in
Tourette Syndrome

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**A dissertation submitted to the School of Graduate and Postdoctoral
Studies of the University of Ottawa as partial fulfilment of the
requirements for the degree of Doctor of Philosophy**

Dissertation Supervisor: Verner J. Knott, D.Phil.

Ottawa, Canada, 2000



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In loving memory of my father,
Hugh Riddock Howson, C.A., Ph.D.

“remember, Anne-Louise, the three keys to a successful PhD....focus, focus, focus”

and

...as told to a dear philosopher friend of mine, “remember Charles, a PhD is not a career”.

ABSTRACT

Tourette Syndrome (TS) is characterized primarily by multiple motor and vocal tics. Additionally cognitive deficits, such as problems with attention, may also exist, in those both with and without co-morbid Attention Deficit/Hyperactivity Disorder (ADHD). Although neuroleptics, which block dopamine receptors, are often the treatment of choice for TS, insufficient symptomatic control often requires the use of increased doses. In addition, undesirable side effects can occur at high doses of neuroleptics, including detrimental effects on attention and concentration. Nicotine has been reported to effectively potentiate neuroleptic-induced catalepsy in rats and, when combined with neuroleptics, to reduce motor and vocal tics in TS patients. However, reported acute and sustained (i.e. up to 8 weeks) nicotine-induced improvements in tic symptomatology in TS patients have come from case reports, open and single blind studies. Nicotine alone has been shown to improve attention and cognition in both normal and neuropsychiatric populations. This double-blind, placebo-controlled, crossover design study investigated the comparative efficacy, both acute and sustained, of placebo and a single test dose of transdermal nicotine patch (TNP) on clinical symptoms of TS (i.e. tics), evaluative ratings (by parents) of attention and maladaptive behaviours, as well as event-related potential (ERP) and behavioural performance measures extracted from a degraded stimulus continuous performance task (DS-CPT) of sustained attention. Twenty-three children and adolescents with TS (with and without co-morbid ADHD), aged 8-17, who were taking conventional neuroleptics (i.e. dopamine D-2 receptor antagonists) were entered into the study.

Adjunctive nicotine, relative to placebo, failed to significantly alter tic symptomatology in either the acute (i.e. 4 hours post-treatment) or follow-up (i.e. 1 week post treatment) conditions. At follow-up but not at acute assessment, parents reported non-specific improvements in attention, and performance was found to have improved on Coding, a visuomotor task measuring freedom from distractibility, following nicotine treatment. Nicotine had a limited effect on area measures of the P300 component of the ERP, by preventing area decrements seen following placebo treatment. However, other performance measures on the DS-CPT, including accuracy and speed of responding, and P300 amplitude and latency measures, failed to identify any significant effects of nicotine relative to placebo. Given the lack of initial significant effects of a single dose challenge of nicotine and the side effect profile of the TNP, the clinical use of adjunctive nicotine in neuroleptically treated children and adolescents with TS appears premature.

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1. INTRODUCTION

1.a. Tourette Syndrome

Tourette Syndrome (TS) is an intriguing, chronic neuropsychiatric disorder of unknown aetiology, which was first described by George Gilles de la Tourette in 1885. The eponymic disorder is characterized primarily by involuntary movements and vocalizations. These motor and vocal tics are usually sudden, repetitive movements, gestures, or utterances that typically mimic some aspect of normal behaviour. They are usually identified as simple or complex. Simple motor tics include eye blinking, shoulder shrugging and head or neck jerking, while simple vocal tics consist of throat clearing, coughing, grunting or snorting. Complex motor tics are generally a stereotyped series of behaviours, often considered to lie on a continuum with compulsive acts, and include facial expressions, grooming behaviours and touching objects or body parts. The Diagnostic and statistical manual of mental disorders - 4th edition (DSM-IV) (1994) requires that "both multiple motor and one or more vocal tic have been present at some time during the illness, although not necessarily concurrently". Although coprolalia, which is considered a complex vocal tic involving the utterance of obscenities, was traditionally considered an integral symptom of the disorder, in fact this occurs in less than 10% of cases (DSM-IV, 1994). The diagnostic criteria of the DSM-IV also require that the tics occur frequently (e.g. daily) and that onset occurs before the age of 18. Typically the anatomic location, frequency, complexity and severity of tics wax and wane over time. The incidence of TS has been estimated at 1.5-3 times higher in males compared to females (DSM-IV, 1994).

1.a.i. History

Tourette Syndrome has had an interesting history. One of the first medically reported cases of an individual with symptomatology, which retrospectively appears to resemble TS, is generally credited to Itard (1825). He described motor tics, barking sounds and uncontrollable utterances of obscenities manifested by a French noblewoman, the Marquise de Dampierre. Sixty years later, neurologist Georges Gilles de la Tourette reviewed Itard's original case and presented eight additional case studies during the weekly lectures of his famous teacher, Charcot (Gilles de la Tourette, 1885). All nine patients manifested brief involuntary movements or multiple tics, six made noises, five shouted obscenities (coprolalia), five repeated the sounds or words of others (echolalia) and two mimicked other's gestures (echopraxia) (Jankovic, 1997). This was the beginning of the official recognition of Gilles de la Tourette syndrome as a distinct neurological disorder. Over the years, the name was shortened to Tourette syndrome and with the DSM-IV (1994), was changed to Tourette's Disorder. Despite this change, the literature continues to use the term Tourette syndrome and for consistency, this will be the convention for this paper. Reviewing the case and family histories of the nine original individuals, Gilles de la Tourette himself first suggested a possible genetic component of the disorder as well as the co-occurrence of obsessive-compulsive symptomatology.

Also in the 1880's, a number of similar reports appeared in the medical literature describing conditions which initially sounded similar to those of Tourette's patients: the "jumping Frenchmen" of Maine (Beard, 1886; Saint-Hilaire, Saint-Hilaire & Granger, 1986), the "latah" of Malaysia (O'Brien, 1883), and the Russian "myriachit" (Hammond, 1884). These "culture-bound syndromes" have since been differentiated from TS as they are considered to

primarily be abnormal startle reactions and occur predominantly in adulthood (Saint-Hilaire, Sainte-Hilaire & Granger, 1986).

Between 1885 and 1965 only 50 or so more cases of TS were officially reported in the medical literature (Shapiro, Shapiro, Bruun & Sweet, 1978). During this time the prevailing psychological movement of psychoanalysis attributed the pathogenesis of TS to a dysfunction in the psyche's ability to repress the forbidden. This conclusion was drawn from the coprolalic and copropraxic content emphasis on profanity, bodily functions and sexual practices (Devinsky & Geller, 1992). Neither psychoanalysis nor a wide variety of psychodynamic therapies were found to be effective in the understanding or treatment of TS.

The aetiology and effective treatment of TS remained a medical mystery until 1961 when Seignot (1961) reported the successful use of haloperidol to reduce the motor and vocal tics of TS. Thus began the new era, the banishment of the unconscious, psychodynamic demons and the origins of the current understanding of the biological basis of TS. The treatment efficacy of a dopamine antagonist provided the first key to unlocking the mysteries of the fascinating primary symptomatology manifested by patients with TS. This moved TS from the domain of psychiatry into the realm of neurology. Subsequent research revealed a high prevalence of co-morbid psychiatric disorders including Obsessive-Compulsive Disorder (OCD) and Attention-Deficit/Hyperactivity Disorder (ADHD), thus re-implicating the psychiatric realm. By the 1980's TS was considered by many to provide the ideal natural paradigm for the investigation of the interaction between emotion and movement (Lees, 1986). Nevertheless, to a large extent, TS still remains an elusive neuropsychiatric puzzle. Despite extensive medical research over the

past 25 years, the apparent heterogeneity of the disorder clouds the waters of discovery into the pathogenesis of this fascinating disorder.

1.a.ii. Epidemiology

Tourette Syndrome was once considered a rare condition and when an international registry of TS incidence was published in 1973, at the time only 174 cases were reported in the USA and 53 cases reported in the UK (Abuzzahab & Anderson, 1973; Robertson, 1994). While the generally reported prevalence of TS is 5 in 10,000 (DSM-IV, 1994), it is unclear how accurate this estimate really is.

There are a number of problems specific to the epidemiologic study of TS. Diagnostic uncertainty is a major limiting factor to the assessment of the true prevalence of TS. Diagnostic criteria, as per the DSM-IV, are based solely on clinical examination and patient history. As of yet, there are no genetic nor characteristic biological markers for TS nor are there neuropathologic anomalies which could confirm the diagnosis post-mortem (Tanner & Goldman, 1997).

The clinical characteristics of TS present a further epidemiological challenge. By definition symptom type and intensity vary greatly between individuals. In addition, the manifestation of tics is often situation-specific, occurring more freely in more relaxed settings, such as at home, with friends or family members. Incredibly enough, the symptoms of TS are often not even recognized for what they are by mildly affected individuals nor recognized in their own family members (Tanner & Goldman, 1997). One of the most difficult aspects of diagnosis

is the ability of individuals with mild or moderate TS to voluntarily suppress or disguise their symptoms for short periods of time, such as at work or school (Jaworski, Boisjoli, Resnick & Bath, 1993). It is also known that tics can diminish greatly or even completely when an individual is actively engaged, as in an interview situation or while playing an instrument. One of the most fascinating examples of this phenomenon is the case of the Canadian surgeon with severe TS and concomitant obsessive-compulsive symptomatology who nevertheless can perform hours of surgery without manifesting any overt tics (Sacks, 1994). Thus a patient may display no symptoms at all while being assessed despite a history of almost continuous tics at home (Jaworski et al., 1993). Diagnosis, particularly in children and adolescents, is further complicated and possibly overshadowed by the additional symptomatology of co-morbid conditions such as ADHD, OCD, affective disorders, learning disabilities and/or other behavioural disorders (Tanner & Goldman, 1997).

Despite these limitations, the prevalence of TS has been assessed in a variety of populations and countries. While estimates vary, Tanner & Goldman (1997) highlight the importance of comparisons of populations that have been matched for age and sex distributions. This is because the symptomatology tends to be greater in children and adolescents between the ages of 8 and 18 while adult symptomatology is comparatively less, due in part to the development of more sophisticated compensatory strategies. Therefore studies with a preponderance of children, who show more overt signs and symptoms of TS, will result in inflated prevalence estimates. The same principles apply to the generally accepted 3:1 male to female sex ratio difference. A final limitation in accurately estimating TS prevalence is inherent

in ascertainment bias. Those who seek medical help or who recognize and acknowledge TS symptomatology will be more likely to be included in estimates.

Given these considerations and epidemiological limitations, the most robust population-based study to date, which employed the most rigorous diagnostic and ascertainment methods thus far, screened 28,037 sixteen and seventeen year old Israelis, during their compulsory military induction evaluation, and estimated a sex-adjusted TS prevalence of 4.28 per 10,000 Israeli 16- to 17- year olds (4.90 per 10,000 for males and 3.10 per 10,000 for females) (Apter et al, 1992).

TS has been reported in cultures and racial groups around the world. The clinical characteristics, demography, family history, co-morbid conditions and treatment outcomes appear to be similar across cultures, providing compelling evidence for an underlying genetic and biological basis to the disorder (Staley, Wand & Shady, 1997).

The frequency of factors found in affected versus unaffected individuals can be compared to identify risk factors for the development of the disorder. Based on a comprehensive review of the epidemiological literature, Tanner & Goldman (1997) suggest that there are three main factors associated with an increased risk for TS: male sex, child or adolescent aged, and a family history of TS. It has also been suggested that school children who initially present with both motor and vocal transient tics or vocal transient tics alone are at a higher risk than others for subsequent development of TS (Bruun & Budman, 1997).

It has frequently been proposed that tic symptoms exist along a continuum, from simple tics associated with transient tic disorder to severe TS. In explanation of this range of

symptomatology, it has been suggested that all tic disorders share a common genetic diathesis (Kurlan, 1994). At present, TS appears to be more common in males than females suggesting the possibility of a sex-differentiated variation in the phenotypic expression of the gene or genes associated with TS. While males manifest more tic and ADHD symptomatology, females manifest more obsessive-compulsive symptomatology (Bruun & Budman, 1997)

1.a.iii. Clinical Characteristics

1.a.iii.1. *Onset*

TS is recognized as a disorder with an onset in childhood. Symptoms or tics have most commonly been reported as beginning between the ages of 2 and 15, with a mean age of onset of 6 to 7 years (Bruun & Budman, 1997). The most frequently reported initial symptoms are simple motor tics involving the eyes (e.g. eye blinking) (Robertson, 1994). Bruun and Budman (1997) reviewed several large studies with a total of approximately 2,400 TS patients and in 50% - 70% of cases facial tics, including the eyes, were the initial symptom. Besides these, in descending order of frequency, the most common presenting symptoms were other simple tics, generally associated with the neck and shoulders, followed by involuntary movements of the upper extremities and finally, much less frequently, were tics associated with the trunk and lower extremities.

Vocal tics, usually consisting of noises such as throat clearing, sniffing, grunting and squeaking, were reported as initial symptoms in only 12% to 37% of TS patients (Bruun, 1988;

Bruun & Budman, 1993; 1997). Robertson (1989) reports that the onset of vocalisations is usually later than that of motor tics, with an average age of onset of 11 years.

1.a.iii.2. *Course*

The very nature of TS is that tics typically wax and wane over time, varying in type, intensity and frequency. New symptoms appear and previous ones remit, either temporarily or permanently. Tics may progress from simple to complex. Simple motor tics, characterized by rapid, darting, involuntary movements, include: eye, nose and mouth movements, facial grimaces, head jerks, shoulder shrugs, arm, hand, leg or foot movements and abdominal tensing. Complex motor tics, which tend to present as slower, more purposeful movements, include: touching, licking, spitting, hitting, jumping, smelling, squatting, retracing one's steps, various forms of self-injurious behaviour, echopraxia (imitation of the movements of others) and copropraxia (involuntary and inappropriate obscene gestures) (Leckman, Towbin, Ort & Cohen, 1988; Robertson, 1994).

Simple phonic or vocal tics generally manifest as fast, "meaningless" sounds, and in addition to those already mentioned, may include coughing, whistling and animal or bird noises. Complex phonic symptoms may be words or phrases and may take the form of echolalia (the imitation of the words or sounds of others) or palilalia (the repetition of the last syllable of a word, a whole word or a phrase in a sentence just spoken by the TS individual themselves) (Robertson, 1994). Coprolalia (the inappropriate and involuntary uttering of obscenities, racist remarks or derogatory name-calling), while often considered the hallmark of TS by the media

and lay population, actually occurs in less than 1/3 of TS patients (Bruun & Budman, 1997), in very few children (Erenberg, Cruse, & Rothner, 1986) and infrequently (2%-4%) in mild cases (Robertson, 1994). Given that only 4% of individuals with TS in Japan (Nomura & Segawa, 1982), compared to 46% and 60% of TS patients in New Zealand (Robertson, Berrill, Mercer, James & Pauls, 1994) and Hong Kong (Lieh-Mak, Chung, Lee & Chen, 1982), respectively, are reported to exhibit coprolalia, it has been proposed that its manifestation is, at least in part, culture-bound.

Other symptoms such as intrusive coprolalic thoughts or mental coprolalia, coprographia, mental palilalia and sensory tics can occur and yet may not be evident, and therefore may be missed unless directly asked about (Bruun & Budman, 1992; Robertson, 1994).

Motor and vocal tics are generally exacerbated by anxiety, stress, boredom, fatigue, and both positive and negative excitement. In addition, premenstrual stress and stimulants such as caffeine, methylphenidate and amphetamines are considered factors that can aggravate tics (Bruun & Budman, 1992; Robertson & Eapen, 1992; Robertson, 1994). More recently, tic and/or obsessive-compulsive symptomatology exacerbations have been reported following certain bacterial and viral infections (Hallet & Kiessling, 1997).

In contrast, tics and vocalizations are often diminished to the point of a temporary disappearance of symptoms, with sleep, alcohol, orgasm, fever, relaxation or absorbed concentration on an enjoyable task (Robertson, 1989). Relaxation can have a paradoxical effect.

At times, as indicated above, it may contribute to a significant reduction in tics. On the other hand, if relaxation follows a period of time during which tics have been suppressed, the

opportunity to relax at home or in privacy may provide the opportunity for tics to be freely expressed, resulting in an increase in both the frequency and intensity of tics (Bruun & Budman, 1992).

1.a.iii.3. *Prognosis*

Nee and colleagues (1980) reported that 40% of 30 adult patients experienced their worst symptoms during the first decade after onset. Not only do symptoms reach their fullest expression in adolescence, symptom type, frequency and intensity are also less predictable, and can change markedly over a relatively short period of time. It has been estimated that approximately one third of individuals with TS experience complete symptom remission during late adolescence - early adulthood. During the same time period, another third improve to the point that their tics are considered mild and relatively unimpairing, while a final third do not appear to experience any significant improvement in their symptoms as adults (Bruun & Budman, 1997).

1.a.iii.4. *Co-morbidity*

The primary symptomatology of TS can often be overshadowed by the behavioural symptoms of conditions that tend to co-occur with TS. The extent of the diversity of associated psychopathology and symptomatology has been debated over the years. Some investigators deny that any specific psychopathology is linked to TS (Shapiro et al., 1978; Shapiro & Shapiro, 1982; Shapiro & Shapiro, 1992), while others contend that a wide variety of psychopathologic

conditions consistently co-occur with TS (Comings & Comings, 1987, 1993). As there does appear to be a higher incidence of the symptoms of depression and anxiety among the clinical population of TS patients, the opposing sides argue whether the co-existence of affective disorders reflect concurrent primary disorders or whether they are secondary to life with a chronic, stigmatising and socially disabling disorder, as TS can be (Robertson, 1989).

While the veracity of the existence of co-morbid affective disorders is still under question, there has been increasing support for the co-existence of co-morbid obsessive-compulsive symptomatology in a greater percentage of individuals with TS than one would expect by chance alone. Gilles de la Tourette himself first described obsessive-compulsive behaviours in the original TS patients (Gilles de la Tourette, 1885). In an early textbook on tics, Meige & Feindel (1907) wrote that the frequency with which obsessions, or at least a proclivity for them, and tics are associated, cannot be a simple coincidence (Leonard, Swedo, Rapoport, Rickler, Topol, Lee & Rettew, 1992). Since that time, the argument for a strong association between obsessive-compulsive symptomatology has garnered both phenomenological (Frankel, Cummings, Robertson, Trimble, Hill & Benson, 1986; Leonard et al., 1992) and genetic (Pauls, Towbin, Leckman, Zahner & Cohen, 1986) support. Estimates of OC behaviour or disorder co-morbidity in TS patients range from 30% to 90% (Como, 1995).

A second co-morbid condition, which has been generally accepted as co-occurring with TS to a significant extent, is ADHD. Robertson (1994) estimates that between 21% and 90% of the clinical TS population, in other words, those who have sought or been referred to medical attention, have co-morbid ADHD. Perhaps due to the more generalizable criteria of ADHD or

due to the fact that ADHD is a much more recently identified disorder than OCD, the genetic association between ADHD and TS is not as clearly established as that of OCD and TS (Robertson, 1994).

Thus the most clearly established co-morbid conditions associated with TS are Obsessive-Compulsive Disorder (OCD) or symptoms (OCS) and Attention Deficit Disorder (with or without hyperactivity) (ADHD) (DSM-IV, 1994). While ADHD has been reported to co-occur in approximately 50% of TS patients (Comings & Comings, 1988) the likelihood of its presence appears to increase with the severity of TS (Jaworski et al., 1993). ADHD alone also tends to be more common in males relative to females. In contrast, OCD alone tends to be more common in females. Co-morbid OCD has been reported to occur on average in approximately 50% of TS patients (Towbin, 1988). Thus, if a TS patient is male and has a co-morbid condition, it will more likely be ADHD while a female TS patient with a co-morbid condition will be more likely to have OCD.

While the association between other behavioural problems and TS has been suggested, the supporting evidence is not as clear or as widespread as it is for OCD and ADHD. These include some forms of self-injurious behaviour, aggression towards others, rages or explosive outbursts, impulsivity, exhibitionism, antisocial behaviours, learning disabilities, separation anxiety and sleep disorders (Jaworski et al., 1993; Robertson, 1994). These other behaviours are often the reason for referral (Robertson, 1994) and thus it must be emphasized that their higher incidence in the TS population may therefore reflect an artefact of referral rather than evidence

for TS as a completely heterogeneous disorder with an increased rate of concomitant neuropsychiatric and psychological symptoms (Robertson, 1989).

1.a.iv. Attentional Deficits

While early clinical and epidemiological studies had suggested that children with TS as a population had a high percentage of attentional and learning difficulties (Cohen, Detlor, Young & Shaywitz, 1980; Jagger et al., 1982), a study comparing attentional and perceptual disturbances in four groups of children: those with TS, ADHD, epilepsy and a normal control comparison group, reported that the TS children differed from the normal children on only 2 of 37 neuropsychological tests used (Harcherik et al., 1982). On a road-tracking task, children with TS did not adapt to changes in speed on the track as quickly as the controls, and their performance on the Coding subtest of the WISC-R was significantly impaired. Of interest is the fact that although these tasks were originally used to assess perceptual-motor vigilance and cognitive functioning respectively, they are now used as measures of attention.

A pattern of poor visual attention span with average auditory attention span was found in seven males between the ages of 9 and 15 (Bornstein, King & Carroll, 1983). Although ADHD was observed to co-occur with TS in 35% and learning problems in 36% of a large series of children and adolescents with TS (N=200), severity of tics was not correlated with increased behaviour and learning problems (Erenberg, Cruse & Rothner, 1986). Van de Wetering, Martens, Fortgens, Slaets & Van Woerkom (1985) found evidence of disturbed concentration alone in 59% and learning difficulties in 47% of their sample of TS patients. Comings &

Comings (1987) compared 246 patients with TS, 17 patients with ADHD, 15 patients with TS+ADHD and 47 normal controls and concluded that the TS patients were significantly different from the controls on signs and symptoms of inattention, impulsivity, hyperactivity, a variety of conduct disorders and schizoid symptoms. As school problems are frequently reported, with children and adolescents with TS falling behind their peers despite normal intellectual abilities (Channon, Flynn & Robertson, 1992), learning disabilities, hyperactivity and ADHD associated with TS may be causing greater problems than the primary symptoms of TS itself (Robertson, 1989). In a comparison of 19 adults with TS and 22 normal controls, on a series of clinical and behavioural measures of attention, the TS group evidenced impairment in sustaining attention and in focussing and shifting set between salient information. These deficits in attention persisted despite statistical control of any potential medication effects (Channon, Flynn & Robertson, 1992).

Randolph, Hyde, Gold, Goldberg & Weinberger (1993) assessed neuropsychological function in 12 pairs of monozygotic twins (MZ) with TS between the ages of 8 and 16, and reported that within twin pairs, the more severe tic symptoms were associated with poorer overall neuropsychological performance and statistically significant differences on tests of attention, visuospatial perception and motor function. In contrast with earlier findings, there was no evidence for a deficit in executive function and performance on the WCST and on a test of verbal fluency did not differ as a result of tic severity. The overall level of neuropsychological performance of all the twins was relatively normal with most test scores close to normative means, many of the subjects tested had only transient tics and, as a control group was not used, it

is difficult to make clear conclusions and to generalize the results to the larger TS population, particularly to those with more severe symptomatology. All subjects were medication free during testing. Five pairs had never used medication and the others were medication-free for at least two weeks prior to testing. Using a continuous performance task (CPT) to assess sustained attention and freedom from distractibility, the group of more severe twins from each pair had significantly fewer correct responses, suggesting that non-genetic factors that effect tic severity may also exert a similar effect on neuropsychological functioning (Randolph et al., 1993). Discriminating between the two groups of differing severity, the CPT was the most sensitive of all the tests administered. The authors suggest that these results contribute to the proposal that attentional disturbances may, in fact, be a cardinal feature of the neuropsychological functioning of individuals with TS.

They also insisted that such neuropsychological indexes of attentional impairment should be considered as distinctly different from the "behavioural" criteria required for a diagnosis of ADHD. Nevertheless, 8 of their twins with TS and 5 of their co-twins also met DSM-III-R criteria for a co-morbid diagnosis of ADHD. It should be noted that along with impulsivity and overactivity, difficulty sustaining attention is one of the three cardinal characteristics of ADHD (Barkley, 1990). Thus it would be important to establish whether TS individuals with and without co-morbid ADHD differ in their performance on attentional tasks such as the CPT.

Addressing the issue of whether neuropsychological deficits in TS are due to co-morbid psychiatric disorders such as ADHD, Yeates & Bornstein (1994) compared the performance of 46 children with TS alone and 36 children with TS and co-morbid ADHD on a battery of

attentional and neuropsychological tests. Since the TS+ADHD group was characterized by more severe complex tics and greater obsessive-compulsive symptomatology, these variables were statistically controlled for in the analysis. The battery of tests administered were chosen in accordance with a theoretical model that divided attention into four dissociable elements referred to as: encode, sustain, focus/execute, and shift (Mirsky, Anthony, Duncan, Ahearn & Kellam, 1991). Based on factor analytic research, each of the 4 attentional elements were linked to different commonly used neuropsychological tests. For example, "encoding" is assessed with the Arithmetic and Digit Span subtests from the WISC-R and WAIS-R; "sustaining" with a CPT; "focusing and executing" with the Coding and Digit Symbol subtests of the WISC-R and WAIS-R respectively, the Trail Making Test and a letter cancellation task; and "shifting" with the WCST (Mirsky et al., 1991; Yeates & Bornstein, 1994). The model proposed by Mirsky et al. (1991) theoretically links these four attentional components to distinct neuroanatomical substrates associated with a putative system of cerebral structures.

Results of the investigation revealed that the TS+ADHD group demonstrated significant deficits in specific components of attention, namely "encoding", "sustaining", and "focussing/ executing". The children with co-morbid ADHD typically performed approximately 1/2 to 1 SD below the norm on the relevant tests while the TS children without ADHD generally performed at or above the norm. The groups did not differ on IQ, non-attentional cognitive skills, or sensorimotor functions. Based on the results, it was concluded that the neuropsychological and attentional deficits associated with TS might often reflect the influence of co-morbid psychiatric disorders associated with TS, such as ADHD and OCD. In other words, the distinct patterns of

neuropsychological functioning may be reflecting pathophysiological processes related to the co-morbid psychiatric conditions rather than reflecting inherent deficits in the tic disorder itself (Yeates & Bornstein, 1994; Silverstein, Como, Palumbo, West & Osborn, 1995). Relating this hypothesis back to Mirsky's model of attentional processes, these independent yet additive dysfunctions may then be reflecting overlapping neuroanatomic substrates (Yeates & Bornstein, 1994).

In order to determine whether attentional disturbance in TS is a stable characteristic of TS or whether it is an artefact of a developmental delay in children with TS which would tend to diminish over time, Silverstein et al. (1995) assessed attentional functioning in adults with TS. In addition, a second research question, regarding the extent to which attentional dysfunction in adults with TS is related to psychiatric co-morbidity, was addressed by comparing 17 adults with TS with 16 adults with co-morbid ADHD and 17 control subjects without any personal or family history of TS, ADHD or OCD. As in children with TS, the deleterious effect of co-morbid ADHD on the attentional functioning of adults with TS was supported. The nature of the attentional dysfunction was similar to that typically found in individuals with ADHD alone. Performance impairment in ADHD is thought to reflect a primary inability to inhibit motor responses to task-irrelevant salient stimuli, as evidenced by a response bias rather than a primary attentional disturbance per se (Copeland & Wisniewski, 1981; Nuechterlain, 1984; Barkley, 1990; Silverstein et al., 1995). In order to parse out cognitive and motor processes associated with the assessment of performance on an attentional task, the use of a degraded stimulus CPT

(e.g. DS-CPT; Nuechterlain, 1984) was proposed for future research as it provides for assessment of response bias and perceptual-attentional impairment (Silverstein et al., 1995).

A further finding in this study was slower reaction times and generally poorer overall test performance in those individuals with TS who reported greater OCD symptomatology in a self-report measure (Silverstein et al., 1995). Although Shuerholz, Baumgardner, Singer, Reiss & Denkle (1996) also reported that three groups of children: those with TS alone, those with TS and a diagnosis of ADHD and those with TS and probable ADHD, all had slowed RTs on measures of attention using choice RT in a Go/No-Go format, they did not assess co-morbid obsessive compulsive symptomatology.

The specific assessment of performance differences on a CPT task of sustained attention compared children with TS with a group of age-matched controls to test the hypothesis that children with TS have an attention deficit (Shucard, Benedict, Tekok-Kilic & Lichter, 1997). The visual CPT used had previously successfully discriminated children with ADHD from normal controls (Halperin et al., 1988). Although significantly slowed RTs characterized 50% of the children with TS, they were as accurate as controls in detecting targets and they made slightly few false alarm errors (Shucard et al., 1997). As the performance profile of the children with TS in this study did not match that of ADHD children, despite being different from normal, it was suggested that the deficit in speed of responding may or may not be due to a deficit in attention. As the RT performance measure reflects cognitive and motor processes, it was further suggested that the differential contributions of each to response slowness in TS would be best assessed with concurrent ERP (e.g. P300) measures of information processing which have been routinely

employed within CPT paradigms as indices of both attentional allocation (P300 amplitude) and processing speed (P300 latency) in psychiatric disorders such as schizophrenia (Nestor, Faux, McCarley, Shenton & Sands, 1990; Cornblatt & Keilp, 1994; Levin, Wilson, Rose & McEvoy, 1996) and ADHD (Klorman, 1991; Corkum & Siegel, 1993; Strandburg et al., 1996).

Shucard et al. (1997) suggest the use of a more demanding CPT task such as a degraded CPT, which would require more effortful sustained attention. Although the CPT task used had previously effectively discriminated differences in children with ADHD from normal controls (Halperin et al., 1990), it was suggested that a more sensitive task may be more effective in detecting attentional deficits in children with TS.

1.a.v. Pharmacological Treatment of TS

Historically, the variety of treatments, which have been tried, and subsequently failed, to effectively treat TS, is quite remarkable. Reviewed (Shapiro et al., 1988) and listed by Shapiro and Shapiro (1996), they include:

"religious treatment such as exorcism and Christian Science; procedures such as cathartics, enemas, emetics, bleeding and other methods of dehydration, hydrotherapy, cold, hot, and tepid douches, warm fomentations, electricity, rhythmic traction of the tongue, thoracic compression, phrenic electricization, static sparks, diet, nutrition, massage, isolation, seclusion, rest, and exercise; drugs such as homeopathic remedies, conium, bromides, chloral hydrate, opium, morphine, laudanum, the basic extract, curare, chloroform, ether, zinc valerianate, valerian, gelsemium, quinine, cannabis indicum, arsenic, mustard plasters, cocaine, kola, coca, condurango, blanco, Cimicifuga nigra, opioids, sedatives, hypnotics, and minor and major tranquillizers; electric and insulin convulsive treatment; surgical treatment such as tonsillectomy, elongation, section, cautery to the vertebral column, or ligature of the spinal accessory nerve, resection of the trigeminal and spinofacial anastomoses, lobotomies, cryothalamectomy, and

chemothalamectomy; and all manner of psychological treatment from psychoanalysis to Erhard Seminars Training (EST)".

The first effective treatment for TS was haloperidol, administered and reported by Seignot (1961) in France and Caprini & Melotti (1961) in Italy (Shapiro & Shapiro, 1996). Since then, haloperidol has been used extensively to treat both children and adults with TS and has been reported to significantly reduce motor and vocal tics in 62-91% of patients (Shapiro & Shapiro, 1996). Additional D-2 receptor antagonists, that have been shown to be effective for the treatment of TS, include pimozide (Sallee, Nesbitt, Jackson, Sine & Sethuraman, 1997), risperidone (Lombroso et al., 1995), olanzapine (Bengi Semerci, 2000), and sulpiride (Robertson, Schnieden & Lees, 1990).

It should be made clear at the outset that usually and ideally individuals with mild TS do not and/or should not require the use of medication for their tics. In these cases, diagnosis, explanation about the nature of the disorder, reassurance, and information about existing self-help groups and information booklets for the teachers of children with TS are often sufficient (Robertson, 1989; Robertson, 1994; Kurlan, 1997). Occasionally pharmacological treatment of co-morbid conditions may be required, particularly when the associated symptomatology is more debilitating than are the motor and vocal tics.

Nevertheless, in cases of moderate or severe TS, pharmacological intervention is often essential, particularly for children and adolescents trying to function effectively in regular classroom and social settings. The role of dopamine in the mediation of the motor symptoms of TS has long been inferred from the therapeutic efficacy of dopamine receptor antagonists, such as

haloperidol, in significantly reducing motor and vocal tics. In contrast, pharmacotherapeutic agents that increase dopaminergic activity, such as amphetamines, l-dopa and methylphenidate, exacerbate tics (Stahl & Berger, 1982). In particular, it is thought that dopamine antagonists with an affinity for dopamine D2 receptors provide the most effective symptomatic relief.

Nevertheless, the fact that neuroleptic treatment has less than 100% efficacy suggests that more than dopamine is involved. While dysregulation of dopamine and acetylcholine neurotransmitter systems are frequently associated with movement disorders, other neurotransmitters or neuromodulators may also be affecting the relevant neural circuits believed to be associated with TS. Currently though, the dopamine antagonists are the treatment of choice, and among them the ones most commonly used to treat TS are haloperidol, pimozide (Shapiro et al., 1989), and sulpiride in the UK (Robertson, Schneider & Lees, 1990; Robertson, 1994). Debates continue regarding the superior clinical efficacy of pimozide relative to haloperidol. Placebo-controlled studies comparing haloperidol and pimozide report support for both the former (Shapiro et al., 1989; Shapiro & Shapiro, 1997), and the latter (Sallee et al., 1997). The clinical management objective in the treatment of TS is to use as little medication as possible to achieve a therapeutic level of symptomatic control while limiting the increased likelihood of adverse events associated with higher doses (Kurlan, 1997).

Another newer neuroleptic agent, risperidone, has potent 5-HT₂ and dopamine D₂ receptor-blocking actions. It has been reported to effectively reduce tic frequency and intensity in children and adolescents with chronic tic disorders (Lombroso et al., 1995) as well as in TS in general (Bruun & Budman, 1996). The purported advantage of risperidone over the traditional

neuroleptics is its serotonin, as well as dopamine blocking properties, which enables it to act on co-morbid obsessive-compulsive symptomatology that is associated with TS, along with the primary tic symptomatology. Despite the theoretical rationale, case reports have suggested that risperidone treatment may in some cases actually increase obsessive-compulsive symptomatology in predisposed individuals (Remington & Adams, 1994). Risperidone is also considered to have a lower risk of inducing extra pyramidal symptoms, which are a concern when higher doses of neuroleptics are required to treat more treatment-resistant tic symptomatology (Kurlan, 1997). Potential extra pyramidal side effects are of particular concern when neuroleptics are used to treat children. Silverstein & Johnston (1987) have reported that although neuroleptics may be indicated, they should be administered cautiously as syndromes similar to tardive dyskinesia were found in 140/410 (35%) of children treated with neuroleptics (Robertson, 1994).

Clonidine, an alpha 2 presynaptic noradrenergic agonist, is often the first treatment initiated for the motor symptoms of TS in order to avoid the potential complications of neuroleptic therapy (Jaworski et al., 1993; Sandor, 1995). Although initial reports of clonidine use in TS suggested significant tic suppressing effects (Cohen, Young, Nathanson & Shaywitz, 1979), double-blind studies have not confirmed its efficacy (Goetz, Tanner, Wilson, Carroll, Como & Shannon, 1987; Goetz, 1992). A number of authors suggest that clonidine is most useful as an initial tic-suppressing agent and for patients in whom behavioural disturbances, such as ADHD, predominate (Robertson & Eapen, 1992; Kurlan, 1997). Clonidine use is associated with fewer and milder side effects and can be administered as a transdermal 1-week patch

(Goetz, 1993). Kurlan (1997) recommends a "start low, go slow" dose titration approach to clonidine and notes that optimal therapeutic efficacy with clonidine may take up to 3 months to achieve.

Although other medications have been tried, with varying success, for the treatment of the motor symptoms of TS (Robertson, 1994), dopamine D2 receptor antagonists, such as haloperidol and pimozide, and the alpha 2 pre-synaptic noradrenergic agonist, clonidine, remain the treatments of choice (Sandor, 1995), where pharmacological treatment is indicated.

1.a.v.1. Cognitive Side Effects of Neuroleptic Treatment in TS

Given the frequent use of neuroleptics to treat TS, an additional pharmacological consideration is the role of associated side effects. Cognitive impairment is a subtle and potentially major limitation of neuroleptic use (Shapiro & Shapiro, 1996). One frequently reported cognitive side effect of neuroleptics is the detrimental effect on attention and concentration when taken at high doses (Werry & Aman, 1975; Shapiro & Shapiro, 1996; Sallee, Rock & Head, 1996). Although the precise mode of cognitive impairment is as yet unknown, Shapiro & Shapiro (1996) describe it as a tranquillizing or akinesic effect that impairs sustained attention and can interfere with motivation and performance at school or work (Werry & Aman, 1975; Mikkelsen, Detlor & Cohen, 1981; Bruun, 1988; Shapiro & Shapiro, 1996). Although the degree of cognitive impairment appears to be dose-related, intellectual dulling or difficulties with attention and concentration have also been reported at very low doses in susceptible individuals (Shapiro & Shapiro, 1996).

In contrast to these reports is the finding by Sallee, Rock & Head (1996) that in a study of 63 children with TS, wherein 44% had a co-morbid diagnosis of ADHD, certain aspects of cognitive functioning actually improved with low dose neuroleptics. In particular, the investigators reported significantly fewer errors of commission on a CPT task in children taking pimozide relative to those taking haloperidol and those in the no-drug group. It is possible that the therapeutic efficacy of neuroleptics for the reduction of motor and vocal tics results in less effort requirements to control or suppress the distracting tics and thereby leaves more motivational and attentional capacity available for the task at hand.

In addition to the findings for and against cognitive side effects of neuroleptics, there have been many studies of the neuropsychological performance of children and adults with TS on a wide variety of tests, which have consistently shown a lack of medication effects (Sand, 1972; Bornstein, 1990; Bornstein, 1991; Bornstein & Yang, 1991; Channon, Flynn & Robertson, 1992; Silverstein et al., 1995; Shucard et al., 1997).

1.a.vi. Nicotine Treatment in TS

A particularly interesting and relatively recent line of research in the treatment of TS is based on the findings that in animals, nicotine, a potent cholinergic agonist, potentiated the hypokinetic effects of neuroleptics (Sanberg et al., 1989; Emerich, Zanol, Norman, McConville & Sanberg, 1991). Thus through the putative stimulation of nicotinic receptors in the brain, adjunctive use of nicotine with dopamine receptor antagonists may provide for improved therapeutic efficacy in the treatment of TS symptomatology.

1.a.vi.1 *Animal Studies*

While both nicotine and the cannabinoids have reportedly long been used to treat extrapyramidal motor disorders on their own (Consroe & Snider, 1986), nicotine and cannabinoids have also been shown to potentiate the effect neuroleptics exert on the motor systems of animals and humans (Moss, McMaster & Rogers, 1981; Sanberg et al., 1989; Moss, Manderscheid, Kobayashi & Montgomery, 1988; Emerich, Norman & Sanberg, 1991). Early animal studies using rats assessed the hypokinetic effects of nicotine, different cannabinoids and dopamine blocking neuroleptics using a behavioural measure of catalepsy, the bar press test (Moss, McMaster & Rogers, 1981; Sanberg et al., 1989). For this measurement, rats were placed in a standing position with their front paws on an elevated bar. The length of time it takes the animals to remove themselves from this unnatural, and presumably uncomfortable, position is taken as a simple measure of hypokinesia or catalepsy, as it is also referred to in the literature. Animals treated with either a vehicle agent or nicotine alone showed negligible hypokinetic effects. In other words, the rats tended to remove themselves from the bar very quickly (approximately <10 seconds). The animals stayed on the bar slightly longer when they were treated with either cannabinoids or the neuroleptics reserpine or haloperidol alone (approximately <50 seconds). In contrast, significantly increased hypokinetic effects (> 1 hour) were observed when the animals were injected with nicotine or cannabinoids after pre-treatment with neuroleptics such as reserpine (Moss, McMaster & Rogers, 1981) and haloperidol (Sanberg et al., 1989; Moss et al., 1989; Emerich et al., 1991).

Comparing three different doses of haloperidol (0.1, 0.2 and 0.4 mg/kg) given in conjunction with a standard dose of nicotine, it was initially reported that the lowest dose (0.1 mg/kg) did not produce the same marked and stable potentiation of haloperidol-induced catalepsy as the higher doses (Emerich et al., 1991). In order to assess whether the lack of effect was due primarily to the limitations of the bar test as a measure of hypokinesia, a more precise, automated monitor, the Digiscan Animal Activity Monitor was subsequently used to assess motor activity. The animals were placed in a chamber and their motor activity was recorded by an automated monitor system which allowed for a more precise assessment of activity using simultaneous, multiple indices including horizontal and vertical activity, average speed and average distance (Sanberg, Giordano, Bunsey & Norman, 1988). It was confirmed that even the lowest dose of haloperidol (0.1 mg/kg) decreased some aspects of movement and that decreases in motor activity were clearly dose-related (Emerich et al., 1991). With this more sensitive locomotor assessment tool, it was shown that even a low dose of nicotine (0.1 mg/kg) significantly potentiated the hypoactivity produced by the lowest dose of haloperidol (0.1 mg/kg). In fact, this combination of nicotine and haloperidol resulted in equivalent levels of hypoactivity as produced by a high dose of haloperidol given alone (0.4 mg/kg) (Emerich et al., 1991). Practically, this finding supports the initial use of low doses of neuroleptics combined with nicotine to achieve the same level of therapeutic efficacy on motor activity which would previously have been found with much higher doses of neuroleptics when administered alone.

1.a.vi.2. Human Studies

To date, while the reports of positive results of nicotine potentiated neuroleptics in TS have been consistent with the results of animal studies, they have come primarily from case reports, open and single blind trials (Sanberg et al., 1988; Sanberg et al., 1989; McConville et al., 1991; McConville et al., 1992; Silver & Sanberg, 1993; Reveley, Bird, Stirton & Dursun, 1994; Dursun, Reveley, Bird & Stirton, 1994; Silver, Shytle, Philipp & Sanberg, 1995; Dursun & Reveley, 1996; Silver, Shytle, Philipp & Sanberg, 1996). Reviewing the published literature to date, acute test doses of nicotine have been administered in the form of chewing gum to a total of 36 patients with TS and as a transdermal nicotine patch (TNP) to a total of 39 patients with TS. The majority of TS patients reported on (55/77) were children or adolescents between the ages of 6 and 18. The majority of patients were on a dopamine-blocking agent such as haloperidol (n=56), pimozide (n=8), perfenazine (n=3), while (n=5) were drug-naïve. Nicotine gum (2mg) was administered as an acute test dose, twice or thrice daily. The application of a single TNP was titrated to deliver either 7mg (USA) or 10 mg (UK) of nicotine in 24 hours. Improvement, defined as a significant decrease in tic frequency or severity, was reported in 64/77 or 83% of TS patients. The positive effects on motor behaviour of a single application of a TNP were reported to last, on average, from one to two weeks (Silver et al., 1996). In one patient, a series of dose-escalated TNP applications given over 6 days in combination with a daily dose of 300mg sulpiride resulted in a significant reduction in tics for up to 8 weeks (Dursun & Reveley, 1996). If the efficacy of nicotine as an adjunctive neuroleptic potentiating agent is confirmed in a double blind placebo controlled study, this treatment strategy would provide the obvious advantage of

requiring less of the neuroleptic and given that nicotine has been shown to be a potent cognitive enhancer in its own right, the combined treatment may serve to improve cognitive/attentional deficits in TS patients.

1.b. **Nicotine**

1.b.i. **Pharmacology of Nicotine**

While cigarette smokers have used nicotine as a drug of addiction for many years, the therapeutic potential of nicotine has only been explored relatively recently. Nicotine does have effects on both the peripheral and central nervous systems, but its' actions on the CNS are of particular relevance to this research study and thus will be the focus of this review.

1.b.i.1. **Pharmacokinetics**

Nicotine is readily *absorbed* from practically every site on or in the body, including: the lungs, buccal and nasal mucosa, skin and the gastrointestinal tract (Julien, 1995). The rate and extent of absorption of nicotine varies with the delivery system used. Inhalation of nicotine facilitates rapid systemic absorption given the large surface area of the alveolar epithelium of the lungs. Similarly, nicotine is easily absorbed through the mucosal membranes of the mouth given a thin epithelium and rich blood supply (Le Houezec & Benovitz, 1991). Available nicotine delivery systems listed in approximate decreasing order of absorption rate include: inhaled smoke, nasal snuff, nasal nicotine spray, oral snuff, chewing tobacco, nicotine lozenge, nicotine chewing gum, non-inhaled pipe and cigar smoke and the transdermal nicotine patch (Russell, 1991; Le Houezec, 1998). Nicotine can also be administered subcutaneously, intramuscularly,

intravenously, or as a rectal suppository, although these latter two delivery systems are primarily associated with animal research. Although transdermal nicotine is less quickly absorbed than the other delivery systems, after an initial delay of 0.25 to 4 hours, a constant rate of nicotine delivery is achieved. With the transdermal nicotine patch (TNP), nicotine bioavailability is approximately 80% and plasma nicotine concentrations remain constant during the application period (Palmer, Buckley & Faulds, 1992).

Nicotine is rapidly and thoroughly *distributed* throughout the body and acts on many different physiological systems, including the central nervous system (CNS) and cardiovascular, respiratory, endocrine, gastrointestinal and skeletal motor systems (Le Houezec & Benowitz, 1991). In general, nicotine has been shown to have a time-related, biphasic effect. Sustained inhibitory effects generally follow initial excitatory effects with acute nicotine administration. Chronic nicotine use has also been shown to have an inhibitory or relaxing effect on skeletal muscle. Nicotine readily crosses the blood-brain barrier through passive diffusion and active transport by the choroid plexus (Oldendorf, 1974) and is distributed throughout the brain, with the highest concentrations in the hypothalamus, hippocampus, thalamus, midbrain, brainstem, and areas of the cerebral cortex (Le Houezec & Benowitz, 1991). Vomiting and nausea are the most common side effects of nicotine use and are caused by nicotine stimulation of the vomiting centre in the brain stem and in the sensory receptors of the stomach. Nevertheless, tolerance to these acute effects develops rapidly with chronic nicotine exposure (Julien, 1995).

Nicotine is extensively *metabolised* by the liver and to a smaller extent by the lungs and the kidneys. Approximately 80-90% of nicotine is metabolised by the liver while 5-10% is

excreted unchanged by the kidneys (Le Houezec & Benowitz, 1991). The major metabolite of nicotine is cotinine. Although plasma concentrations of cotinine are higher than those of nicotine, cotinine does not appear to have any significant CNS contributory effects. Cotinine is further metabolised to 3-trans-hydroxy cotinine. Nicotine does not appear to accumulate in the body and elimination half-life of transdermally administered nicotine ranges from 3 to 6 hours (Palmer, Buckley & Faulds, 1992).

1.b.i.2. Pharmacodynamics

Nicotine binds to cholinergic receptors in both the CNS and peripheral nervous system (PNS) (Palmer et al., 1992). There are two main types of cholinergic receptors: nicotinic and muscarinic. They have been named for the ability of the two natural alkaloids, nicotine and muscarine, to mimic the effects of acetylcholine as a neurotransmitter (Le Houezec & Benowitz, 1991). Nicotine binds stereospecifically to nicotinic cholinergic receptors in the autonomic ganglia, adrenal medulla, neuromuscular junctions and the CNS (Palmer et al., 1992).

Two different nicotinic cholinergic subreceptors have been well characterized, C10 (muscle) and C6 (neuronal) receptors, while additional subreceptors continue to be identified. Nicotinic cholinergic subreceptors at the neuromuscular junction are selectively blocked by the antagonist decamethonium, hence the name C10. Other nicotinic receptors are selectively blocked by mecamlamine in the PNS and the CNS or by hexamethonium in the PNS only, and are therefore called C6 receptors (Le Houezec & Benowitz, 1991). Nicotine effects on the CNS are primarily

attributable to the C6 nicotinic subreceptors, which have a high affinity for both nicotine and acetylcholine (Clarke, Schwartz, Paul, Pert & Pert, 1985).

Following binding, a biphasic response occurs. A low dose of nicotine acts as a cholinergic agonist, while a high dose results in an initial agonist effect followed by a prolonged period of antagonism (Palmer et al., 1992). Nicotine acts both pre-synaptically and post-synaptically. Activation of presynaptic nicotinic receptors facilitates the release of acetylcholine, while post-synaptically, nicotine has excitatory effects. Chronic stimulation of nicotinic receptors causes the upregulation of nicotinic receptors, by either an increase in number or by a shift in proportion of low affinity to high affinity binding sites (Nordberg, 1995). Nicotine receptor upregulation has been shown to occur in both animal and human brains (Benwell & Balfour, 1985; Benwell, Balfour & Anderson, 1988) and is thought to be due to nicotine-induced receptor desensitisation. The initial desensitisation of nicotinic receptors may also reflect a biological compensatory strategy given the natural toxicity potential of nicotine.

In addition to the direct action of nicotine on cholinergic receptors, nicotinic receptors are also located on presynaptic dopaminergic and serotonergic neurons. Nicotine stimulation of these receptors results in the release of dopamine and serotonin (Jarvik & Schneider, 1992). Other neurotransmitters, neuromodulators and hormones are indirectly affected by nicotine, including: norepinephrine, epinephrine, GABA and glutamate, cortisol, prolactin, growth hormone, arginine, vasopressin, B-endorphin and adrenocorticotrophic hormone (Pomerleau & Pomerleau, 1984).

Nicotine's main mechanism of action in the brain is as a cholinergic agonist and by stimulating cholinergic receptors in the CNS, nicotine produces increases in electrocortical arousal and psychomotor speed (Sherwood, Kerr & Hindmarch, 1992), as well as improvements in sensorimotor performance, memory consolidation, attention and vigilance (Warburton, Rusted & Fowler, 1992). Of additional interest is nicotine's mediating effect on dopamine transmission. It is nicotine's ability to bind to nicotinic receptors on mesolimbic dopaminergic neurons (Clarke & Pert, 1985) that likely contributes to the powerful reinforcing effects of nicotine. Although nicotine's reinforcing effects resemble those of cocaine and the amphetamines, nicotine's action is indirect and thereby results in a lower level of dopaminergic stimulation in the reinforcement areas of the brain (Julien, 1995). In addition it appears that nicotine binding to nicotinic receptors located on nigrostriatal dopaminergic neurons (Clarke & Pert, 1985) has potentially beneficial effects on the clinical symptoms of TS through nicotine potentiation of the effects of dopamine receptor antagonists such as haloperidol.

1.b.ii. Nicotine and Cognition: Animals

Due to the ethical limitations on nicotine research in drug-naïve humans, nicotine research in experimental animals provides many advantages, including: random assignment to experimental conditions, assessment of differential dosing, particularly for high dose effects, acute versus chronic dosing in both drug-naïve and chronic use animals, as well as post mortem neuropathological investigations of treatment effects (Levin, 1992).

The nicotinic cholinergic agonist, nicotine, has frequently been shown to improve learning and memory in experimental animals while the nicotinic antagonist, mecamylamine, has been shown to impair memory on the same types of experimental tasks (Levin, 1992). As not all findings have been positive, Levin (1992), who has expertly and comprehensively reviewed the research in this area, has suggested that discrepancies in reports of nicotine effects on animal cognitive performance may be attributable to the differential effects of a number of factors, including: variations in dosage levels, genetic and sex differences, individual differences in best-dose response, the nature of the task used, acute versus chronic dosing and the persistence of nicotine effects.

Although nicotine dosage levels appear to have significant differential effects in experimental animals, in general, low doses facilitate performance and high doses either have no effect or actually impair performance. Low doses of nicotine have been found to improve both passive and active avoidance performance in rats and mice (Haroutunian, Barnes & Davis, 1985; Oliverio, 1966) while on the active avoidance task, high doses of nicotine have a negative effect on performance.

Genetic factors and sex differences may also play a role in determining nicotine effects on the performance of cognitive tasks. For example, the hippocampi of different strains of mice have been found to have different nicotine binding patterns (Marks, Rom, Campbell & Collins, 1989). In addition, certain strains of mice, which have been inbred over a number of generations, were reported to be more sensitive to the enhancing effects of nicotine on avoidance conditioning tasks (Bovet, Bovet-Nitti & Oliviero, 1966) and on visual discrimination tasks, with the poorer

performing strains generally showing the greatest improvement (Bovet-Nitti, 1966, Bovet-Nitti, 1969; Levin, 1992). Differential effects of nicotine have also been reported between the sexes within the same species and strain of animal. In a particular strain of mice, nicotine caused a greater retrieval deficit in female mice on a relearned active avoidance response paradigm (Gilliam & Schlesinger, 1985). Inter-individual differences within the same species and strain of experimental animals can also contribute to the heterogeneity of nicotine response at the same and different dosages.

Performance effects following acute doses of nicotine have varied with the nature of the task used for the assessment of performance. Initial working memory deficits on a memory task assessing choice accuracy were attributed to nicotine-induced proactive interference (Dunnet & Martel, 1990). A later replication study, using a similar protocol except for increased inter-trial intervals intended to reduce task-related proactive interference, failed to find any detrimental effects on working memory due to nicotine (Bushnell, personal communication in Levin, 1992).

Chronic administration of nicotine has also been found to improve memory performance. Rats trained on a working memory paradigm, using an eight-arm radial maze, were treated with either nicotine or a placebo over a 3-week period. The nicotine treated rats showed significantly faster learning relative to controls and evidenced no tolerance to the cognitive enhancing effects of nicotine over time (Levin & Rose, 1990; Levin et al., 1990). In many chronic nicotine administration studies there appears to be a delay in the onset of facilitating effects of nicotine (Nelsen, 1978; Levin, 1992). Nevertheless, once the facilitating effects of nicotine appear, they tend to persist for an extended period of time, even when nicotine administration stops altogether

(Buccafusco & Jackson, 1991; Levin & Rose, 1990; Levin et al., 1990, 1992). Cognitive facilitation of performance on memory tasks was reported in rats that were pre-treated with nicotine for 3 weeks compared to untreated controls even when training only began one week after nicotine was withdrawn. After an initial delay of onset, the nicotine treated rats showed enhanced learning on a radial-arm maze task relative to controls. Although the controls did catch up to the nicotine treated rats, the significant differences in learning and memory performance between the two groups does provide support for persistence of nicotine effects rather than solely as a drug contribution to improved learning when nicotine is administered during the learning of the task (Levin, 1992; Levin et al., 1992). The time course of delayed onset of nicotine facilitating effects may be correlated with the upregulation of nicotinic receptors following chronic administration. Chronic administration with nicotine has been shown to result in a shift in the proportion of high and low affinity binding sites (Romanelli, Ohman, Adem & Nordberg, 1988; Zhang et al., 1994) as well as an increase in the number of nicotinic receptors in a given brain region (Levin, 1992). Since the time course of the upregulation of nicotinic receptors has been shown to follow a similar time course as that of the ameliorative effects of chronic nicotine administration on cognitive performance tasks, improved cholinergic neurotransmission may be responsible (Levin, 1992). Alternatively or additionally, dopaminergic systems in the cortex, striatum and ventral tegmental area (VTA) are considered to play a critical role in cognitive functioning and are indirectly affected by nicotinic stimulation. Nicotine has excitatory effects on the densely populated nicotinic receptors located on dopamine cell bodies in the substantia nigra and the VTA, while nicotinic stimulation of highly concentrated nicotinic receptors on

dopamine terminals in the striatum facilitates the release of striatal dopamine (Levin, 1992). In contrast, administration of nicotinic antagonists (e.g. mecamylamine) to these same areas inhibits dopamine release (Ahtee & Kaakola, 1978; Haikala & Ahtee, 1988). Levin (1992) reports that nicotinic cholinergic receptors interact more closely with dopamine D2 subreceptors than with other dopamine subreceptors. Choice accuracy on the radial-arm maze test is impaired with administration of the nicotinic blocker, mecamylamine. This effect is further potentiated with a dopamine D2 blocker (McGurk, Levin & Butcher, 1989) and is reversed with a D2 agonist (Levin, McGurk, South & Butcher, 1989) while D1 ligands evidenced no effects (Levin, 1992).

1.b.iii. Nicotine and Cognition: Humans

When a diverse sample of smokers was asked why they smoked, a common response was that smoking helped them to think and to concentrate (Russell, Peto & Patel, 1974; Warburton and Wesnes, 1978). In a survey of both light and heavy male and female smokers who smoked at work (Meade & Wald, 1977), it was found that 56% of their daily cigarette consumption occurred during the workday. In addition, the highest hourly rates of cigarette smoking occurred immediately after lunch and then again at approximately 3:00 p.m. In both time frames, smoking presumably helped or was perceived to help increase focussing and concentration on work tasks when the body was most taxed, after lunch, or the mind most fatigued, towards the end of the workday. It is the nicotine, rather than the cigarette or the action of smoking itself, which appears to be the main objective of smoking behaviour. When smokers were given unmarked cigarettes containing different levels of nicotine, they varied their inhalation and puffing

techniques accordingly (Guillerm & Radziszewski, 1978; Sutton, Russell, Feyerabend & Saloojee, 1978). For example, unmarked, low-level nicotine cigarettes, resulted in smoking behaviour characterized by more frequent puffs and longer and deeper inhalations. This finding suggests that smokers use smoking strategies to achieve optimal individual levels of nicotine absorption. Therefore a number of different findings suggest that, in many instances, smokers appear to use nicotine for its beneficial effects on attention by using it to improve their performance on tasks that require efficient mental processing (Warburton & Walters, 1989).

Empirically, assessing nicotine effects on performance in humans provides the opportunity for determining with greater specificity the effects of nicotine on varying aspects of cognition compared to that possible with animals. On the other hand, unlike animal research, until recently most of the human nicotine research was limited to the effects of nicotine in smokers given the ethical restrictions on administering nicotine to non-smokers. Despite many reports of nicotine's enhancing effects on a variety of cognitive functions, including attention (Wesnes & Warburton, 1983; 1984; Warburton & Walters, 1989; Wesnes, 1987), memory (Peeke & Peeke, 1984; Rusted, Graupner & Warburton, 1995) and psychomotor performance (Petrie & Deary, 1989; Hindmarch, Kerr & Sherwood, 1990; Kerr, Sherwood & Hindmarch, 1991; Bates, Mangan, Stough & Corballis, 1995) in nicotine deprived smokers, fewer studies have assessed nicotine effects on cognitive functioning in non-smokers (Hindmarch, Kerr & Sherwood, 1990; Le Houezec et al., 1994). Among the smokers, it is often difficult to parse out the differential contributions to performance improvements of the relief of nicotine withdrawal symptoms and true cognitive enhancement. Difficulty concentrating and impaired performance

are key symptomatic features of nicotine withdrawal. In fact, the desire to alleviate these withdrawal symptoms, among others, as well as the desire to achieve the perceived behavioural and psychological benefits of smoking are often responsible for the high relapse rates among smokers trying to quit (Heishman, Taylor & Henningfield, 1994). Thus significant improvements in performance among smoke-deprived smokers may simply be reflecting a re-instatement of pre-deprivation levels of performance. Although this issue has been partially addressed by findings of performance above baseline levels in non-deprived smokers who have been administered additional nicotine (Pritchard, Robinson & Guy, 1992), the results of nicotine effects on cognitive performance have continued to be debated. Smokers as a group may differ from non-smokers in terms of basic neurochemistry or on any number of other psychobiological factors (Levin, 1992). These potential pre-determined confounds would therefore limit the generalizability of the effects of nicotine in smokers to the non-smoking population. In addition, in a comprehensive review of performance effects in human nicotine studies (Heishman et al., 1994), the authors noted the following limitations in many of the studies reviewed: placebos were often not used, pre-existing plasma nicotine concentrations were unknown or not reported and precise dosing was not easily controlled when cigarettes were used as the mode of delivery for nicotine. The authors cautioned that besides rigorous experimental methodology, findings of nicotine administration resulting in statistically significant cognitive or performance facilitation in either non-smokers or non-deprived smokers relative to their baseline performances would be required to support the notion that nicotine acts as a cognitive enhancer (Heishman et al., 1994).

Nicotine effects on human performance have been assessed in the following areas of cognitive functioning: sensory and motor abilities, learning, memory and attention. Reviewing a total of 101 studies published in scientific journals between 1970 and 1993, Heishman et al. (1994) assessed the findings reported in the studies based on the previously defined criteria. In other words, while many studies reported positive findings, Heishman et al (1994) based their conclusions only on studies where absolute enhancement from nicotine was supported by the inclusion of pre-deprivation performance data, placebos, and a sufficient number of supporting results to justify the generalizability of results. Based on these criteria, they concluded that in non-deprived smokers and non-smokers, of all the areas of performance and cognitive functioning assessed, nicotine's cognitive enhancing effects were most clearly supported in the areas of motor and attentional functioning. Nicotine administration appeared to reliably increase the finger-tapping rate, a measure of motor ability, in both nicotine-deprived smokers and non-smokers.

1.b.iv. Nicotine and Cognition: Neuropsychiatric Populations

Nicotine's cognitive enhancing effects have also been reported in neuropsychiatric populations. In senile dementia of the Alzheimer type (SDAT), subcutaneously administered nicotine produced dose-related improvements in signal detection performance during a rapid visual information processing (RVIP) task such that the performance of patients approached the performance of a healthy elderly control group. Nicotine also produced improvements in reaction time relative to baseline and placebo performance on the same task (Sahakian, Jones,

Levy, Gray & Warburton, 1989; Jones, Sahakian, Levy, Warburton & Gray, 1992). These findings further support the hypothesis that nicotine modulates vigilance and stimulus evaluation aspects of discrimination in information processing tasks (Sahakian et al., 1989), possibly by way of enhanced cholinergic transmission.

The neurochemical effects of nicotine have been described as being qualitatively similar to many of the stimulant medications used to treat ADHD (Coger, Moe & Serafetinides, 1996). Nicotine, like the psychostimulants methylphenidate and dextroamphetamine, acts as an indirect dopamine agonist and thereby contributes to improved attention and increased arousal (Conners, Levin, Sparrow, Hinton & Erhardt, 1996). In adults with ADHD, it has been reported that the psychological and behavioural effects of nicotine directly result in a reduction in the symptoms of ADHD (Coger et al., 1996). In an acute double-blind crossover study of adult ADHD, transdermal nicotine or placebo patches were administered to smokers and non-smokers with ADHD. While there were subjective reports of increased concentration and vigour from the participants, there was also objective evidence of improvement on chronometric measures of attention and timing accuracy (Conners et al., 1996). In a similar design, transdermally administered nicotine to adult smokers and non-smokers with ADHD resulted in an overall significant reduction in reaction time on the CPT. In the smokers, nicotine also reduced variability in reaction time over CPT trial blocks (Levin et al., 1996b).

When nicotine was administered transdermally to schizophrenic patients who were concurrently being treated with haloperidol, nicotine resulted in a dose-related reversal of haloperidol-induced impairment on memory and complex RT tasks. In addition, with the CPT,

nicotine ameliorated attentional deficit by reducing the variability of responding over time (Levin et al., 1996a).

In Tourette syndrome, nicotine administered with neuroleptics has anecdotally been reported to improve attention and concentration. Thus far, systematic, objective assessment of the effects of nicotine in TS has not been reported in the literature.

1.b.v. Nicotine and Attention

Attentional abilities can be further classified into selective, divided, focussed and sustained attention. Rather than representing a unitary process, different types of attention require different types of cognitive processing. Selective attention requires the ability to focus attention on a given stimulus dimension while ignoring other distracting or intruding stimuli or stimuli dimensions and divided attention requires a conscious shift from processing information from one source to processing that from another (Warburton & Walters, 1989). Sustained attention requires selective monitoring of target stimuli, usually with a required psychomotor response to small infrequent changes in stimuli presented, over a long period of time (Warburton, 1992). Vigilance tasks are the classic paradigms for measuring sustained attention and can be further categorized based on the period of time focussed or sustained attention is required. In reviewing the nicotine and human performance literature, Heishman et al. (1994) differentiated focussed and sustained attention based on the amount of time spent attending to one task or aspect of information in a given task. *Focussed attention* was the designation given to tasks

lasting less than 10 minutes, with an average length of time of 5 minutes, while tasks identified as requiring *sustained attention* were those lasting for more than 10 minutes.

After reviewing the investigations of nicotine's effects on selective, divided and focussed attention, Heishman et al. (1994) made the following conclusions. There was more support in favour of, rather than against, improvement in selective attention in nicotine-deprived smokers who were administered nicotine. With non-abstinent and non-smokers, four of five studies reported that nicotine either had no effect or actually impaired performance on measures of selective attention. By 1994, only 5 studies directly assessed nicotine effects on divided attention and the consensual results were similar for deprived, non-deprived and non-smokers. Nicotine appeared to enhance tracking performance by decreasing tracking errors but had no clear effect on reaction time (Heishman et al., 1994). Seventeen studies were included in the review of nicotine effects on focussed attention (Heishman et al., 1994). In deprived, non-deprived and non-smokers, the majority of studies reported no positive nicotine effects on either the recognition or the motor components of the required responses.

Of all the areas of human performance and cognitive function assessed for the effects of nicotine administration, the area most relevant to this research study is nicotine's effects on attentional abilities and more specifically, nicotine's effects on sustained attention. More studies have assessed nicotine's effects on sustained attention than any of the other defined dimensions of attention and these studies on sustained attention have also revealed more positive support for nicotine's ameliorative effects than in any of the other areas. There are three key features of vigilance tasks requiring sustained attention: 1) directed attention with selective monitoring of

stimuli presented, 2) attention is sustained over long periods of time, and subjects are required to 3) detect and respond to small, infrequent changes in input (Warburton & Walters, 1989).

Vigilance can be assessed in either the auditory or the visual mode. The majority of vigilance performance paradigms measure sustained attention using visual stimuli. Another essential component of vigilance paradigms relates to the third key feature, that there is a relatively low probability of a target appearing. Thus subjects are required to maintain a constant level of readiness to respond over time. Primary measures used to assess performance on vigilance tasks are the "hit rate", the "false alarm rate" and the reaction time of response. The hit rate refers to the number of correct responses to target stimuli as a proportion of the total number of target stimuli, while the false alarm rate reflects the number of incorrect responses to either an absence of stimuli or to distracting, non-target stimuli on a given trial. Reaction time is usually monitored electronically for precise measurement of the time taken to respond to a given target stimuli. Reaction time tasks require subjects to press a button as quickly as possible whenever they are presented with the target stimulus. Vigilance paradigms differ from simple choice reaction time tasks as they are performed and analysed over a longer period of time, with performance assessed as a function of time. Vigilance tasks are therefore considered to be a more sensitive index of the ability to sustain attentional effort over time. Although early vigilance tasks required subjects to attend and respond to stimuli for up to 80 minutes, more recently the time has been shortened to a minimum of 10 minutes as it has been found that under most circumstances, performance measures assessed over a period of at least 10 minutes can provide reliable estimates of a given subjects' ability to sustain attention. Typically, during a

vigilance session, the detection rate decreases, as measured by either a decrease in the hit rate or an increase in reaction time over time, and is referred to as the vigilance decrement (Warburton & Walters, 1989).

Vigilance tasks can be used to measure sustained attention, as indexed by the speed and accuracy of cognitive processing over time. The vigilance decrement, determined by hit and false alarm rates, is an index of sustained attention while RT provides an estimate of information processing efficiency. Typically the hit and false alarm rates of the vigilance decrement are analysed using signal detection theory (Grier, 1971) to determine whether a decrease in vigilance is due to a change in stimulus sensitivity (*A Prime*) or a criterion shift (*Beta*). Stimulus sensitivity refers to an individual's ability to accurately perceive target stimuli while criterion shift refers to the criteria upon which subjects make decisions regarding their response to a given stimulus. Stimulus sensitivity is considered to be reduced when the hit rate decreases over time while the false alarm rate does not. The subject has become less sensitive to the stimuli and is therefore not detecting target stimuli with the same accuracy as they had been in the earlier stages of the task. If both hit rate and false alarm rate decrease over time during a given vigilance task, according to signal detection theory, this is interpreted as representing a criterion shift. This apparent change in response criterion generally reflects a change in the subject's expectancy of the target stimuli to appear. Criterion shifts occur therefore when the probability of target stimuli occurring increases or decreases. For instance, when the probability of a target stimulus increases from 20% to 50%, of the total number of stimuli presented, subjects will generally

make more errors of both omission, or target misses, and commission, or incorrect responses to non-targets.

Although different types of tasks have been used to assess vigilance, the three most commonly reported in the nicotine literature, as reliable measures of the vigilance decrement, are: 1) the Mackworth Clock task (Mackworth, 1950), 2) three digit sequences (Bakan, 1959) and 3) the CPT (Rosvold, Mirsky, Sarason, Bransome & Beck, 1956). The Mackworth clock requires subjects to detect and respond to brief pauses in the movement of the minute hand on a clock (Warburton, 1992). In the second type of vigilance task, commonly referred to as a rapid visual information processing task (RVIP), a series of digits are presented sequentially on a screen in rapid succession and subjects are required to detect three digit sequences of odd or even numbers (Warburton, 1992). The third type of vigilance task, the CPT, often requires less complex cognitive processing and is therefore more ideally suited to the assessment of children or cognitively impaired individuals. In the original CPT task (Rosvold et al., 1956), subjects were required to identify and respond to a clearly presented target letter (e.g. X) from other clear non-target letters presented briefly and successively at a rate of one every 920 milliseconds (ms). The difficulty of the CPT can be increased by: 1) shortening the duration the stimulus is presented, 2) decreasing the probability of the target stimulus occurring and 3) varying the nature of the stimuli presented such that the difficulty of their detection is increased. In one version of the CPT, the degraded stimulus continuous performance task which stresses encoding (DS-CPT) (Nuechterlein, Parasuraman & Qiyuan, 1983), stimuli are degraded or blurred so that they are

more difficult to perceive. Such changes in the stimuli increases the level of task difficulty by increasing the processing load required for accurate stimulus encoding.

Most of the early studies of nicotine's effects on human cognitive performance used cigarette smoking as the means of nicotine delivery to the brain. On vigilance tasks such as the Mackworth Clock test and the RVIP, both of which have been shown to produce reliable vigilance decrements, beneficial effects of nicotine have been documented (Wesnes & Warburton, 1978; Wesnes & Warburton, 1984). Smoking in a group of smokers helped to reduce the decrement in vigilance while maintaining stimulus sensitivity to target stimuli in an 80-minute visual vigilance task. In contrast, in a comparative group of smokers who were not allowed to smoke and a group of non-smokers performing the task, both groups evidenced a vigilance decrement characterized by a reduction in stimulus sensitivity (Wesnes & Warburton, 1978). Nicotine's enhancing effects on human performance on vigilance tasks have been reported for both light and heavy smokers as well as for smokers who had not been nicotine deprived (Wesnes, Warburton & Matz, 1983). In an attempt to control for the effects of smoking itself, smokers were given either nicotine-containing cigarettes or sham cigarettes which contained no nicotine. Smoking sham cigarettes resulted in a decrement in vigilance while the effect of nicotine-containing cigarettes was to significantly decrease this vigilance decrement during an 80-minute auditory vigilance session (Wesnes & Warburton, 1978). The investigators also found that when smokers were given cigarettes containing different levels of nicotine, the higher nicotine cigarettes produced the greatest effects, while the performance of the smokers receiving cigarettes containing negligible amounts of nicotine approximated that of smokers not

smoking. Since higher nicotine delivery cigarettes appear to improve performance more than low delivery ones, this supports the contention that it is the nicotine that is the ingredient in cigarettes from which the positive effects are derived. As previously mentioned, studies which evaluate nicotine's effects on cognitive performance using cigarettes as the means of nicotine delivery in smokers have been criticized for both their limited generalizability to the general, non-smoking population and the potential confound of primary effects reflecting reversal of nicotine withdrawal rather than cognitive enhancement per se. Therefore, in order to confirm that the putative positive effects of nicotine on sustained attention over time were specifically due to nicotine, nicotine has also been administered in the form of tablets, gum, nasal spray and subcutaneous injections. In smokers who abstained overnight prior to testing, nicotine tablets reduced the vigilance decrement that occurred over time in a placebo controlled design, again by maintaining stimulus sensitivity (Wesnes et al., 1983). When nicotine tablets were given to both light and heavy smokers and to non-smokers, the results provided further support for an enhancing effect of nicotine on vigilance type tasks (Warburton & Wesnes, 1989). As similar effects were found in non-smokers and in smokers with significantly different smoking habits the first concern regarding the generalizability of results was countered. While many studies have not reported positive findings, the more methodologically rigorous studies, using nicotine tablets (Wesnes et al., 1983), nicotine gum (Parrott & Winder, 1989; Parrott & Craig, 1992) and most recently, nicotine administered in subcutaneous injections (Le Houezec et al., 1994; Foulds, Stapleton, Swettenham, Bell, McSorley & Russell, 1996), have repeatedly reported that nicotine appears to enhance human information processing by increasing or maintaining hit rate over time

without significantly affecting the false alarm rates. These findings therefore suggest that increased stimulus sensitivity is the main mechanism for the reduction in the vigilance decrement. This fits with the stimulus sensitivity and response criterion components of signal detection theory as the probability of target stimuli being presented does not generally change during most vigilance tasks reviewed. If we recall that response criterion changes with expectancy then given adequate practice on the task, the subject's expectancy of the target stimuli will not be likely to change over the duration of the task and thus their response criterion could not be expected to shift significantly. We are also able to conclude that nicotine results in an absolute improvement in cognitive efficiency since nicotine not only prevents the vigilance decrement in non-smokers but also improved the performance of non-deprived smokers above baseline levels (Wesnes, 1987). Thus the criticisms of early nicotine research in smokers that nicotine was merely relieving the detrimental nicotine withdrawal effects on cognitive processing appear to be largely unfounded.

Nicotine also appears to decrease or maintain the speed of reaction time over the duration of vigilance tasks. Thus the increased accuracy of the hit rates does not appear to be the result of a speed-accuracy trade-off. As speed of responding is decreased or maintained over time and accuracy of responding over time is increased on vigilance tasks, such as the RVIP and CPT, subsequent to nicotine administration, it has been suggested that the level of cognitive efficiency has been improved both quantitatively and qualitatively (Wesnes, 1987). Since nicotine appears to maintain or increase stimulus sensitivity relative to situations of non-use and as nicotine can decrease reaction time without necessarily affecting motor processes per se, it has been proposed

that nicotine acts by speeding up stimulus evaluation processing (Le Houezec et al., 1994; Knott, Kerr, Hooper & Lusk-Mikkelsen, 1995; Houlihan, Pritchard & Robinson, 1996a; 1996b).

Of interest is the finding that medium rather than high doses of nicotine appear to provide the greatest improvement in sustained attention. An inverted-U explanation of nicotine effects on performance has been proposed (Wesnes & Warburton, 1983; Parrott & Craig, 1992). An optimal level of nicotine results in optimal levels of performance while too little or too much nicotine appears to result in suboptimal performance.

Based on animal research, it has been proposed that, on a neural level, nicotine acts by maintaining cholinergic release subcortically by acting presynaptically on the ascending pathways from the reticular formation to the cortex, thereby increasing cortical arousal (Wesnes, 1987). While scopolamine, a cholinergic antagonist, decreases electrocortical arousal, nicotine has been shown to counteract the scopolamine-induced deficits on the RVIP and Stroop test when they are given concurrently (Wesnes & Revell, 1984). Also, in both animals and humans, electro cortical arousal has been shown to be directly correlated with behavioural efficiency (Wesnes, 1987). Thus one of the most enduring explanations for nicotine's enhancing effects on sustained attention tasks suggests that the effects are due to cholinergic effects on cognitive processing via increased electrocortical arousal. Additionally, it has been suggested that nicotine may be increasing arousal and improving attention through its' actions as an indirect dopamine agonist (Conners et al., 1996).

1.c. Event-Related Potentials

"ERPs are voltage changes recorded from the human scalp that are time-locked to a sensory, motor, or cognitive process, and therefore provide an electrophysiological window onto brain function during cognition."

Mangun & Hillyard, 1995, p. 43

The main advantage of ERPs over other physiological measures of human brain activity, such as CT, PET and MRI scans, is the high degree of temporal resolution achievable with ERPs.

ERPs are averaged segments of EEG which are selected as occurring immediately prior to and/or following a given sensory, cognitive or motor stimulus or event. The resulting event-related potentials therefore are considered to reflect the brain's response directly following the stimulus or event in question. This series of positive and negative deflections is usually identified according to their relative timing following the event: early, middle and late potentials.

The early or exogenous potential peaks elicited in auditory tasks are traditionally identified by Roman numerals from I to VI and occur between 0 and 10 milliseconds (ms) following the event.

These very early potentials are also referred to as brain stem potentials, in reference to their origin. Middle or mesogenous potentials or components occur between 10 and 100 ms and are identified as N or P for a negative and positive deflection, respectively. In ERP research, a negative deflection is up and a positive deflection is down. These middle potentials, which are alternatively subsumed under an exogenous label by many authors who use an exogenous-endogenous dichotomy, conventionally are further identified by lowercase letters (i.e. o, a or b).

The late, endogenous potentials occur between 100 and 1000 ms following the same event and

are generally identified with an N or a P followed by a numerical reference to the latency of the peak (e.g. N100 for a negative deflection peaking at 100 ms post-event). The characteristic patterns of brain waves following events or stimuli associated with different experimental paradigms have been correlated with different stages of human information processing.

The most basic dichotomy is between exogenous and endogenous components of the human event-related potential. Amplitudes and latencies of exogenous components occurring within 100 ms of the stimulus or event reflect early neural processing of the features of the stimulus presented and are therefore responsive to changes in the physical characteristics of the stimulus (e.g. intensity, duration and inter-stimulus interval [ISI]). Given this link to physical feature analysis, the scalp distribution of the potentials is determined primarily by the sensory system activated. In contrast, the late, endogenous potentials often referred to as cognitive evoked potentials, are not obligatory responses to physical stimuli rather their elicitation depends on the nature of information processing required by the subject. Endogenous potentials are associated with the cognitive processing of a stimulus or event rather than with the stimulus or event per se (Knott, 1989). Conscious, motivated cognitive processing, such as selectively attending to or making a decision about a particular stimulus will thereby modulate the amplitude, the latency or the scalp distribution of the evoked waveform. Variations in ERPs can in turn provide us with information about the theoretical intracranial functional processes underlying cognitive psychological processes.

1.c.i. P300 Wave

The P300 wave is a positive deflection in the human ERP which occurs approximately 300 ms after a given event or stimulus. The events or stimuli can be presented in different modalities such as visual, auditory or somatosensory. What distinguishes the endogenous P3 component of the human ERP from the earlier exogenous components, which generally occur < 80-100 ms following the "event" in question, is the psychological nature of the subject's interpretation of the stimulus rather than simply a reaction to the physical characteristics of the stimulus (Sutton, Braren, Zubin & John, 1965). The most reliable experimental design used to elicit the P300 wave is the "oddball paradigm". Two different stimuli or events are presented to the subject in the same modality. One of the events occurs more frequently and is therefore referred to as the "standard". The second event, pre-identified as the "target" event, occurs with much less frequency, hence the name "oddball". The subject is given instructions to ignore the standard event and to respond to the target event. Responses can be either overt and motoric, such as pressing a button, or covert and cognitive such as having the subject silently count the number of target events. Unattended, task irrelevant and novel stimuli can result in a P300 subcomponent of small amplitude, a latency between 220 and 280 ms and fronto central scalp distribution (Pritchard, 1981). This is referred to as the P3a and its amplitude varies with the degree of physical contrast between the novel stimuli and background stimuli as well as the probability of the novel stimuli occurring. In contrast, the P3b sub-component of the P300 wave is elicited by attended, task relevant target stimuli. The P3b amplitude is larger and is maximal centroparietally between 310 and 380 ms. The amplitude of P3b is inversely related to relative

probability of the stimulus class and the complexity of the target stimuli in contrast with the non-target stimuli. It has been proposed that the more frontal P3a occurs primarily to noticed novel, but unattended events while the more parietal P3b requires active attention to a relevant task (Pritchard, 1981). In auditory selective attention studies, where separate oddball series are presented dichotomously to left and right ears, P300 is only elicited by the attended, rare stimuli and not to the unattended or ignored rare stimuli. Therefore, when the subject is told to ignore the stimuli or events presented to them, the P3b generally does not occur. On the other hand, when the subject is instructed to watch or listen for the pre-identified target among a random series of standard stimuli, then the P3b generally occurs following positive identification of the target stimuli. In other words, the P3b only occurs when the subject is actively engaged in, or attending to, the task of detecting target events (Picton, 1992). It is this attention requirement for the elicitation of the P3b that makes the P3b an attractive tool for assessing changes in attention. In the rest of this document as in most of the literature, the term P300 wave will refer solely to the parietal P3b component.

While the average amplitude of the P300 wave is approximately 10 μ v in alert, normal controls (Picton, 1992), P300 amplitude can range from 5 to 20 μ v (Coles & Rugg, 1995). The amplitude of the P300 wave is thought to be affected by a number of factors including: stimulus probability, task complexity, stimulus complexity, and task difficulty (Picton, 1992). The average P300 latency for healthy, young adults responding to a simple task would occur at 300 ms post-stimulus. The latency of the P300 wave can occur anywhere between 200ms and 800ms and is positively correlated with level of difficulty with which an event can be categorized as a

target event (Picton, 1992). As latency is longer with greater difficulty in event categorization, it has been proposed that P300 latency can be used as a measure of stimulus evaluation time (Coles & Rugg, 1995; Donchin and Coles, 1988), which is independent of response-related (i.e. selection, activation and execution) processing.

1.c.i.1. Physiological Characteristics of the P300

A minimum of three electrodes placed on the midline of the scalp (Fz, Cz, and Pz) is required to record a P300 wave (Picton, 1992). The amplitude and latency of the P300 wave vary at different points on the scalp. The amplitude of the P300 wave occurs maximally over the parieto-central area and the latency of the P300 wave decreases at more frontal locations on the scalp. Although the source(s) of the P300 is as yet undetermined, there has been evidence implicating the limbic system, thalamus and basal ganglia (Picton, 1992). It is most likely that multiple neural generators, rather a single source, are responsible for the elicitation of the P300 (Johnson, 1993).

1.c.i.2. Psychological Aspects of the P300 wave

1.c.i.2.a. P300 amplitude variations

When a randomly ordered series of stimuli are presented and the subject is told to attend only to one type of stimuli, the P300 occurs only in response to task-relevant, target stimuli (Picton, 1992). This implies both an attention and a task-relevant requirement for the elicitation of the P300. Further, when subjects are performing concurrent tasks in a dual task paradigm,

Wickens, Kramer, Vanasse & Donchin (1983) showed that as the perceptual demands of the secondary task increase, the amplitude of the P300 evoked by the detection of targets in the primary task decreases in amplitude (Picton, 1992). In contrast to this effect of increased perceptual demands, increased motor demands of the secondary task do not significantly affect the amplitude of the P300 (Israel, Wickens, Chesney & Donchin, 1980). Thus, P300 amplitude reductions to target stimuli in a primary task are inversely proportional to the increased perceptual difficulty of identifying target events in the competing task (Klorman, 1991; Donchin, Miller & Farwell, 1986; Kramer, et al, 1988). Based on these findings, P300 amplitude can be perceived as an index of applied attentional resources based on the perceived relevance of the target stimulus to the task at hand or as Picton (1992) suggests, intuitively, the P300 amplitude seems to reflect the amount of conscious attention paid to a stimulus.

The difference between two types of stimuli is conventionally described in terms of the probability of the occurrence of each of the stimuli and the size of the P300 wave is generally greater when the stimulus or stimulus category is less probable (Picton, 1992). Target events reliably produce P300s of significantly greater magnitude when they occur less than or equal to 30% of the time in relation to the standard events with 70% occurrence (Duncan-Johnson & Donchin, 1977). As the "surprise" nature of the odd or target stimulus or event appears to be the critical trigger for the P300 wave, the sequence of stimuli immediately preceding the target stimulus is as important as the probability of the occurrence of the target itself (Duncan-Johnson & Donchin, 1977). In other words, P300 amplitude will be greater to a target event that occurs after a series of non-target events. In contrast, P300 amplitude will be attenuated following the

same target event presented immediately after one or more other target events. Probability is not limited to the relative proportion of time one stimulus type is presented relative to the total stimulus presentation time. Stimulus probability can also vary as a function of stimulus type or category (e.g. 20% of the stimuli are of a different kind than the other 80%). Picton (1992) emphasizes that it is important to note that it is the probability of the category assigned to a particular stimulus by the subject (e.g. target versus non-target) rather than the probability of the individual stimulus, which explains the effects of probability on the P300 amplitude. Despite the different types of stimulus probability that can elicit P300s, it has been suggested that the P300 wave is more closely related to temporal rather than stimulus probability (Fitzgerald & Picton, 1981).

When the task of discriminating target from standard stimuli becomes increasingly difficult, the amplitude of the P300 becomes smaller while its latency increases (Picton, 1992). With increased latency reflecting greater stimulus evaluation time, it has been proposed that the decrease in amplitude reflects a decreased level of confidence with which the target is discriminated (Squires, Hillyard & Lindsay, 1973). On the other hand, amplitude can also decrease when the task becomes too easy and the subject ceases to focus on the task at hand (Hillyard, Squires, Baver & Lindsay, 1971). From this perspective, P300 amplitude could also represent the amount of useful information present in a given stimulus, both in terms of the relevance and the reliability of the information to the task at hand (Johnson & Donchin, 1978). Other authors have suggested that P300 amplitude reflects the amount of information received during perception, which is a function of both the information transmitted and any information

lost through "equivocation" during its processing (Ruchkin & Sutton, 1978; Picton, 1992). In order to achieve a P3 of maximum amplitude then, a given task would have to be difficult enough to require sufficient attentional resources be allocated to it, and yet achievable enough to enable the subject to complete it with a level of confidence which would be sufficiently reinforcing to the subject.

The "triarchic" model of P300 amplitude variations (Johnson, 1986) was developed to incorporate the variety of stimulus and subject variables that have been proposed to affect P300 amplitude. Three major factors, identified as information transmission, subjective probability and stimulus meaning, independently and interactively contribute to the final P300 amplitude. The triarchic model asserts that initially, between the P300-eliciting "event" and the resulting P300, the amount of information transmitted by the event is affected by two variables: inattention and equivocation. Insufficient allocation of attentional resources will have a direct effect on the amount of stimulus information received by the subject. Equivocation refers to the amount of information lost through uncertainty on the subject's part about having correctly perceived a given event, as a target or a non-target event for example. Given the independent effects of these two variables, the balance of information transmitted is proposed to then have a multiplicative effect on the sum of the other two major factors identified by the model: subjective probability and stimulus meaning. As previously mentioned, there is a well-documented inverse relationship between the subjective probability of an event and the associated P300 amplitude. This probability can be described in terms of both global probability, a priori probability of the target event relative to that of non-target events, and local probability, the particular sequence of events

immediately preceding the P300 eliciting event (also referred to as sequential expectancies). According to the model, stimulus meaning, the third major factor contributing to P300 amplitude, is further comprised of three variables: task complexity, stimulus complexity, and stimulus value. In general, P300 amplitude independently increases with task complexity, stimulus complexity and with stimulus value. The triarchic model does successfully integrate many of the different hypothetical constructs that have been proposed to affect the amplitude of the P300. In addition, as Picton (1992) points out in his review of the P300, while some of the details of the model can be debated, the importance of the model lies in its proposal that the P300 itself is likely the result of several different processes rather than reflecting a unitary phenomenon. Considering these different processes, it is proposed that the sum total of contributing factors allows for the interpretation of P300 amplitude as an index of subjective attention and involvement in a given task.

1.c.i.2.b. P300 latency variations

Latency changes have long been interpreted as reflecting the difficulty of discriminating the target stimulus from non-target stimuli (Picton, 1992). In a simple oddball task, average P300 wave latency for alert, healthy subjects occurs approximately 300 ms post-target event. Latency increases with more difficult tasks. The difficulty of the task refers to the degree of stimulus evaluation required rather than the type of response required. When a subject is asked to respond to a target event in some way, by pressing a button for example, in a simple oddball task paradigm, the RT can occur earlier than the peak of the P300 (Ritter, Simson & Vaughan,

1972). It was therefore concluded that the P300 could not represent the decision process that invoked the response (Picton, 1992). The effects of response bias on P300 latency and overall reaction time have been evaluated by having the subjects place their response emphasis on either speed, at a cost to accuracy, or accuracy, at a cost to speed (Kutas, 1972). P300 latency was unaffected by the speed versus accuracy instructions while the subject's reaction time was significantly altered. When speed was emphasized, reaction time occurred prior to P300. When accuracy was emphasized, reaction time was equal to or later than P300. In other words, P300 latency and RT were more closely correlated when the subjects were asked to emphasize accuracy rather than speed of responding (Kutas, McCarthy & Donchin, 1977). When accuracy was the objective, the RT often followed the peak latency of the P300. These findings support the contention that P300 is a measure of stimulus evaluation time and Kutas et al. (1977) have further suggested that the P3 may in fact index the completion of stimulus evaluation. During an easy task, or one where speed is the objective, subjects will often respond before they are absolutely sure their response is accurate. On the other hand, a more difficult task, or one where accuracy is required, will result in more equivocation which requires longer stimulus evaluation time to resolve, in order to increase the subject's sense of certainty that a response is correct.

1.c.ii. P300 and TS

There is a dearth of published literature on the P300 in TS. In a task-based auditory oddball paradigm with two conditions, with and without a motor response component, P300 amplitude and latency did not differ between adult TS patients and controls. Both groups had

larger P300 amplitudes in the motor rather than in the non-motor, counting condition. The P300 amplitude increase in the motor condition was more pronounced in the patient compared to the control group (Van Woerkom, Fortgens, Rompel-Martens & Van de Wetering, 1988). In a sensory ERP paradigm using an auditory oddball task, where no response was required, no significant differences were found between the P300s of a heterogeneous TS patient group and a normal control group. When patients with TS alone were compared to TS patients with either co-morbid ADHD or co-morbid OCD, it was reported that those with co-morbid OCD has significantly shorter P300 latencies compared to the other two groups. P300 amplitude variations were not reported (Drake et al., 1992). Thus far, there have been no published ERP in TS patients on a sustained attention task.

1.c.iii. P300 and ADHD

The most consistent finding in the event-related potential research on children and adolescents with ADHD is of smaller P300 amplitudes, relative to normal controls, in response to target stimuli on sustained attention tasks, such as the CPT (Klorman, 1991). Besides improving behavioural aspects of ADHD, psychostimulants such as methylphenidate, have also been shown to increase P300 amplitudes on CPT tasks, relative to placebo (Klorman, Brumaghim, Fitzpatrick & Borgstedt, 1991; Verbaten et al., 1994). P300 latencies have also been reported to be longer in children with ADHD, relative to control subjects (Strandburg et al., 1996), and again, treatment with methylphenidate has been shown to have an ameliorative effect

by shortening the latency of P300 to both target and non-target stimuli (Klorman et al., 1991).

1.c.iv. P300 and Nicotine

Given the findings of nicotine-enhanced performance on cognitive tasks assessing sustained attention, it is important to discern how these improvements occur. Time-locked brain ERPs elicited in response to specific sensory and task events provide the means to determine what sensory/attentional/cognitive processes are more or less affected by nicotine. ERPs in smoking/nicotine performance research have generally been studied within two major types of paradigms, sensory and task-based ERP studies (Knott, 1989).

The former, sensory studies, measure the differential effects of the brain's responsivity to sensory stimuli in eyes-closed/eyes-open non-task conditions subsequent to nicotine administration. Brain reactivity measures of nicotine's effects on neuroelectric response to sensory stimuli have primarily been assessed in nicotine deprivation or non-deprivation conditions in smokers. Following a comprehensive review of the findings, Knott (1989) proposed that smoking/nicotine deprivation appears to reduce the brain's responsivity to changes in the intensity of the physical properties of sensory stimuli, as evidenced by changes in exogenous ERPs, while acute smoking/nicotine administration increases central responsivity to sensory stimuli. These findings provide support for the widely held proposal that the cognitive enhancing effects of smoking/nicotine may be achieved through increased central arousal levels.

The second major type of paradigm for the elicitation of ERPs is the task-based paradigm. Endogenous ERPs are elicited in task-based paradigms that require active cognitive processing

and decision-making, as changes in amplitude and latency of endogenous ERPs are determined by the psychological processes elicited by the stimuli rather than by the physical properties of the stimuli. The P300 ERP component is optimally elicited when adequate allocation of cognitive resources result in the accurate evaluation of infrequently occurring target stimuli among a series of more frequently presented non-target stimuli. As previously mentioned, changes in the P300 latency are generally interpreted as reflecting variations in the time taken for the completion of accurate stimulus evaluation and classification, while changes in P300 amplitude are thought to reflect the differential allocation of attentional resources. As P300 latency is considered to be relatively independent of response processes, P300 latency effects can therefore be linked to specific stages of information processing.

Nicotine's effects on P300 latency were assessed by Herning & Pickworth (1985) in an auditory oddball task conducted under either low or high continuous white noise conditions. Following 12 hours of nicotine deprivation, eight smokers were pre-treated with either mecamylamine, a nicotinic cholinergic antagonist, or a placebo. Subsequent to this, nicotine gum was administered in 0mg, 4mg or 8mg doses. At baseline, high intensity noise had the effect of prolonging P300 latency to correctly identified target stimuli. Neither of the pre-treatment conditions alone, placebo or mecamylamine, had any significant effects on P300 latency. The negative noise effect on P300 latency was significantly reduced by the 8mg nicotine dose but not by the 0mg or 4mg doses of nicotine gum. Mecamylamine did not block the 8mg-induced P300 latency reduction.

P300 amplitudes were also differentially affected by nicotine dose, mecamylamine pre-treatment and conditions of high or low noise. In the low noise condition, following placebo pre-treatment, P300 amplitude was increased with 4mg nicotine gum while P300 amplitude was decreased following mecamylamine pre-treatment. In the high noise condition, following placebo pre-treatment, both the 4mg and the 8mg doses of nicotine gum decreased P300 amplitude while P300 amplitude was increased by both doses following mecamylamine pre-treatment. The P300 latency findings suggest a facilitatory effect of nicotine on stimulus evaluation aspects of cognitive processing in deprived smokers in distracting circumstances (Knott, 1989). The P300 amplitude findings were interpreted as providing empirical evidence supporting the subjective reports of smokers that smoking helps to improve their concentration (Herning & Pickworth, 1985).

Assessment of the ERP effects of smoking in an RVIP sustained attention task provided further evidence for nicotine-induced improvements in stimulus evaluation as indexed by P300 latency (Edwards, Wesnes, Warburton & Gale, 1985). Nineteen smoking-deprived, habitual smokers were administered three treatment conditions: 0.9mg or 1.5 mg nicotine delivery cigarettes or a non-smoking condition. A 10-minute pre-treatment baseline RVIP testing session preceded a 10-minute treatment phase. This was followed by a 20-minute post-treatment RVIP session. By increasing stimulus sensitivity, the two nicotine doses offset the vigilance decrement and, in addition, they speeded reaction time compared to the three baseline levels and the non-smoking condition. In addition, smoking/nicotine significantly reduced P300 latency in the first 10 minutes of the RVIP following treatment, compared to baseline and non-smoking conditions.

The significant effects of smoking on P300 latency reductions in the first 10 minutes of the 20 minute RVIP were thought to parallel the maximal nicotine levels achieved in the brain during the same time period. No significant effects, in either direction, were observed for P300 amplitude. The authors interpreted these results as providing empirical support for the use of smoking by smokers as a psychological tool for the enhancement of cognitive performance (Edwards et al., 1985).

Another study assessed nicotine effects on the RVIP in smokers differing in carbon monoxide (CO) absorption following smoke inhalation (Michel, Nil, Buzzi, Woodson & Battig, 1987). Following 5 hours of abstinence, smokers were tested before and after smoking their preferred brand of cigarette. P300 latency changes were not reported while P300 amplitudes were quantified as an area measurement or magnitude rather than the more commonly used peak amplitude. Both RVIP performance measures and P300 amplitude magnitudes increased after smoking and were unaffected by the amount of CO absorption. The same investigators assessed the effects of a 4mg dose of nicotine or placebo gum in deprived smokers on a subject-paced version of the RVIP (Michel, Hasenfratz, Nil & Battig, 1988). No significant effects on performance, reaction time, P300 latency or amplitude were found.

The effects of smoking were also examined on ERPs and performance in subject-paced RVIP, assessed under no-noise and noise conditions (Hasenfratz, Michel, Nil & Battig, 1989). Smoking-deprived smokers were assessed during two baseline test sessions and then again in two post-treatment test sessions. Treatment consisted of either smoking one preferred brand cigarette over a 10-minute time period or a control condition during which subjects relaxed without

smoking. During the second test session after the treatment condition, six disturbing noise bursts were presented. P300 amplitude was increased in the smoking group relative to the non-smoking group in the no noise test session only. During the noise condition, both correct responses and false alarm errors increased in the control group relative to the smoking group. The authors concluded, "without smoking, noise leads the subjects to evaluate the stimuli less carefully and to react with less control". This may be interpreted as smoking/nicotine providing a protective effect in a distracting environment, perhaps by activating a stimulus filter or stimulus gating mechanism, as previously proposed by Knott (1986), in distracting circumstances or when attentional demands are high.

While the results of these studies are compelling, their generalizability is limited by the fact that nicotine's effects were studied in smokers only. As P300 amplitude reductions early in a non-smoking period are returned to pre-cessation baseline levels when smoking subjects resume smoking (Herning, Pickworth & Cone, 1986), it has been suggested that smoking deprivation in smokers may result in a transient attentional impairment which is rectified by smoking. Knott et al. (1995) compared cigarette smoking with sham smoking and although no significant differences in amplitude were found, cigarette smoking resulted in significantly decreased auditory P300 latencies relative to the sham smoking condition.

Addressing the issue of whether nicotine's cognitive enhancing effects are absolute or whether they merely reflect the removal of negative withdrawal symptoms in deprived smokers, Le Houezec et al. (1994) measured the effects of low doses of subcutaneous nicotine in non-smokers performing a visual choice reaction time task, in which both stimulus and response

complexity were manipulated. After baseline performance measurement and a no treatment control session, twelve non-smokers were administered subcutaneous injections of either 0.8mg of nicotine or 0.8ml of saline. Although performance was measured both 15 and 45 minutes post injection, only the 15 minute post treatment results were significant. Nicotine, relative to the control condition, but not the saline condition, speeded reaction times without resulting in a speed/accuracy tradeoff. Nicotine treatment significantly decreased P300 latency in the most difficult task condition, i.e. high stimulus and response complexity. P300 amplitude was increased in both the nicotine and the saline conditions relative to the control condition when no injection was given, suggesting the possibility of an anticipatory placebo effect on attention. However, in a more recent study of smokers, utilizing the same task as Le Houezec et al. (1994), a single oral dose (21mg) of nicotine was found to shorten reaction times and increase P300 amplitudes irrespective of stimulus and/or response complexity (Knott, Bosman, Mahoney, Ilivitsky & Quirt, 1999).

From the ERP studies measuring nicotine's effects on P300, there appear to be fairly consistent reports of significant reductions in P300 latency, and to a lesser extent increases in P300 amplitude, suggesting that the mechanisms through which nicotine appears to have its cognitive enhancing effects on tasks measuring selective and/or sustained attention include enhancement of processing speed and/or a more efficient allocation of processing/attentional resources. As previous work by Knott (1986; et al., 1995), has suggested that the enhancing effects of nicotine on the efficient cognitive processing of task relevant stimuli, as evidenced primarily by decreases in P300 latency, may be due to the activation or facilitation of a gating or

filtering mechanism for distracting or task irrelevant stimuli, a series of studies manipulating auditory task variables were conducted (Knott et al., 1995). Consistent with previous findings, in a simple auditory oddball counting task, cigarette versus sham smoking resulted in significant P300 latency reductions. A lack of significant effects on P300 amplitudes was interpreted as resulting from the ease of the cognitive task, which would not necessarily have required the additional attentional benefits accorded by smoking/nicotine. The implications of these findings complement previous recommendations for task conditions that require high levels of attentional demand for the elicitation of increased P300 amplitudes. Alternatively, P300 amplification may be induced with less difficult tasks in individuals with limited attentional resources (Knott et al., 1995).

In two additional studies from the same laboratory, the effects of smoking on P300 were examined by manipulating attention with auditory distractors (Knott et al., 1995). In a study paradigm where auditory, deviant stimuli were randomly distributed among target and non-target stimuli, P300 amplitude was found to be increased following cigarette smoking while no significant effects were observed for P300 latencies. In a subsequent study paradigm involving non-random strategic placement of auditory deviant stimuli immediately before target stimuli, in the smoking condition, there was a significant decrease in P300 amplitude that was not affected by the cigarette smoking. There was a significant reduction in target detection rates and non-significant slowing of reaction time to target stimuli, which were preceded by an auditory deviant stimulus. The findings were interpreted as suggesting that smoking/nicotine may exert

differential effects on the processing of target stimuli under conditions of distraction (Knott et al., 1995).

In a comparison of smoking/nicotine effects on P300 indices when stimuli are presented in different modalities, Houlihan et al. (1996a) administered visual and auditory oddball tasks to two groups of smokers. Following overnight smoking abstinence, subjects were tested pre and post smoking low (0.05mg) and high (1.1mg) nicotine cigarettes or after a non-smoking condition. Subjects were also tested following the smoking of a second high nicotine yield cigarette (1.1mg). Reaction time was decreased to both visual and auditory targets following smoking of the high yield cigarette (1.1mg). In the visual oddball task, P300 latency was significantly decreased after the high yield but not after the low yield or non-smoking condition. The effect was maintained after the second high yield cigarette. There were no significant effects on P300 latency for the auditory task and smoking had no significant effects on P300 amplitude in either the visual or the auditory task. However, when the subjects were separated into low and high CO absorption groups, P300 amplitude was increased following the first high yield cigarette in subjects with higher CO absorption.

The decrease in P300 latency following smoking/nicotine in a visual oddball task replicates a fairly consistent finding. Since reaction time decreased in both auditory and visual tasks, the investigators interpreted this finding as indicating a significant contribution of nicotine to improved motor processing on cognitive tasks requiring a motor response. They further suggest that the enhancing effects of nicotine on stimulus evaluation aspects of cognitive processing in visual tasks may be due in part to the relatively greater contribution of nicotinic

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receptors in the visual compared to the auditory cortex (Houlihan et al., 1996a). This suggestion has received some recent support from a study investigating P300 effects of acute nicotinic and muscarinic cholinergic blockade with single doses of mecamylamine (20mg) and scopolamine (0.1mg), respectively (Knott, Harr & Ilivitsky, 1999). Although no P300 latency effects were observed, nicotinic receptor blockade, but not scopolamine blockade, attenuated P300 amplitudes in a visual but not in an auditory task.

1.d. Summary and Rationale

Nicotine has been reported to effectively potentiate neuroleptic-induced catalepsy in rats and to reduce motor and vocal tics in TS patients treated with neuroleptics. Thus far the reports of enhanced response with nicotine supplementation have come from case reports as well as open and single blind trials. The primary aim of this clinical study was to examine the acute (4 hours post-administration) and sustained (1 week post-administration) effects of a single dose of transdermal nicotine within a double blind, placebo-controlled study in neuroleptically treated children and adolescents with TS. Problems with attention have also been reported in TS children both with and without co-morbid ADHD. Besides largely anecdotal reports of improved attention and concentration in TS subjects who have had nicotine added to their usual neuroleptic medication, thus far research in acute nicotine treatment of TS has focussed primarily on the clinical (e.g. tics) assessment of the effects of the treatment. Nicotine treatment effects on attention have not thus far been specifically assessed in children and adolescents with TS, who are taking concurrent neuroleptics. Nicotine given alone has been shown to improve attention and cognition in normal populations and nicotine given in combination with neuroleptics has been reported to attenuate neuroleptic-induced cognitive deficits in schizophrenia. In addition to the monitoring of clinical response with objective measures, this study objectively assessed the attentional impact of the treatment combination using parent-completed rating scales measuring behavioural change and performance, and ERP indices of sustained attention acquired in a CPT task paradigm. The CPT behavioural performance measures included both response accuracy

and response speed indices, and the ERP measures included amplitude (and area), and latency of the P300 component, reflecting attentional allocation and processing speed, respectively.

1.e. Hypotheses

1. Neuroleptically-treated children and adolescents with TS would exhibit acute and sustained (i.e. follow-up) reductions in the frequency and intensity of motor and vocal tics following the administration of a single dose of nicotine.

2. Neuroleptically-treated children and adolescents with TS would exhibit acute and sustained (i.e. follow-up) improvements in attention and concentration at home, based on behavioural reports from parents, following the administration of a single dose of nicotine.

3. Neuroleptically-treated children and adolescents with TS would exhibit acute and sustained (i.e. follow-up) improvements in behavioural performance (i.e. improved response accuracy and decreased reaction time) on the CPT as well as enhanced CPT-related P300s, as evidenced by increased amplitudes/areas and/or decreased latencies following the administration of a single dose of nicotine.

2. METHOD

2.a. Study Subjects

Twenty-three children and adolescents (19 boys/ 4 girls, mean age=12.0; SD=2.8), with a principal diagnosis of TS according to DSM-IV criteria (APA, 1994), were entered into the study. Subjects were recruited through referring physicians, affiliated with the Tourette Syndrome Clinic of the Children's Hospital of Eastern Ontario (CHEO), the Neurology department of the Children's Hospital of Eastern Ontario (CHEO), or the Child Psychiatry department of the Royal Ottawa Hospital. Neurological and psychiatric evaluations and diagnoses, conducted to establish inclusion and exclusion criteria, were carried out by the referring physicians. Three subjects were diagnosed with TS alone, while 20 subjects had co-morbid ADHD. Additional co-morbidity included: obsessive-compulsive symptomatology (n=7), learning disability (n=2), conduct disorder (n=1), oppositional defiant disorder (n=1), and Asperger's disorder (n=1). All subjects, except one, had been stabilized on neuroleptic medication prior to participation in the study. One subject, who was not taking a neuroleptic, was included in the original study sample. Characteristics and medication dosages of the total sample of children and adolescents originally entered into the study (n=23) are outlined in Table 1a, while the characteristics of the final study sample (n=14) are profiled in Table 1b.

Initially eligible for the study were subjects who met the following inclusion and exclusion criteria:

2.a.i. Inclusion Criteria:

1. Male or female subjects, who met DSM-IV criteria for TS, between the ages of 8 and 17 years of age.
2. Had a diagnosis of moderate or marked TS as per TS-Clinical Global Impression Scale (Appendix A).
3. Must have been taking dopamine receptor blockers for at least two weeks prior to nicotine administration.
4. Motor and vocal tics were not adequately controlled on current medication regimen.
5. Must have had a negative smoking history as well as live in a non-smoking environment to avoid smoke exposure from active and passive smoking, respectively.
6. Must have been able to understand and communicate with the investigator.
7. Must have been reliable and agreed to cooperate with all tests and examinations in the protocol.
8. Subject's parent or guardian must have given informed consent in writing and subject must have signed informed assent form.

2.a.ii. Exclusion Criteria:

1. Organic brain disease, known head injury or history of seizures.
2. Serious or progressive illnesses, including: cardiovascular, hepatic, renal, respiratory, haematologic, endocrinologic, dermatologic, or neurologic disease (not including TS) or a clinically significant laboratory value.
3. Any previous severe allergic reactions to medications.
4. Cardiac arrhythmias including first-, second-, or third-degree cardiac blocks, severe bradycardia (<50 beats per minute), or other types of arrhythmias, including non benign arrhythmias, active coronary ischemic disease, cardiogenic shock, heart failure, history of electrocardiogram (ECG) evidence of acute myocardial infarction or chronic, unstable angina (physical examination would have been carried out by the referring physician, and ECG at the study site - the Royal Ottawa Hospital).
5. Bronchospastic pathologies such as bronchial asthma, chronic bronchitis, or emphysema.
6. Diabetes mellitus requiring insulin or oral hypoglycaemic agents.
7. Subjects weighing less than 25 kg.
8. Pregnant or lactating females.

2.b. Study Design (Study Design Flow Chart – Appendix B)

Subjects attended the laboratory for one orientation session, two acute (i.e. single) dose test sessions and two follow-up sessions, each one-week after the respective acute dose test session. The initial test session involved clinical and attention assessments carried out before

and after the double-blind administration of a single placebo patch or a single transdermal nicotine patch (TNP). Subjects, who were taking their usual dopamine receptor antagonists, were randomly assigned to either the TNP or placebo treatment condition. Half of the subjects were randomly assigned to receive the placebo treatment in the first test session and the nicotine treatment in the second test session. The remaining half of the subjects received the treatment in the reverse order. The follow-up sessions, one week after each of the test sessions, involved re-assessment of clinical symptoms and attentional measures without any nicotine or placebo treatment being given. The two test sessions were separated by 8 weeks.

2.c. Study Procedure (Acute Test Session Schedule – Appendix C)

During the orientation session, which took place 1-2 days prior to the first test session, while the subjects were practising the computerized (CPT) task in the laboratory, their parent or guardian was in an adjoining room filling out the Child Behaviour Checklist (CBCL) (Appendix D). For the 7-day period prior to each of the test sessions parents or guardians were asked to assess tics and other behaviour using the following questionnaires:

<u>Rater</u>	<u>Questionnaire/Scale</u>
a) Parent or guardian:	Tourette Syndrome Symptom List (Appendix E)
b) Parent or guardian:	Conners' Parent Rating Scale - Revised: Long Version (CPRS) (English) or Conners' Parent Questionnaire (French) (Appendix F)

On each of the two acute dose test days, subjects arrived at the laboratory (8:30 a.m.) after having abstained overnight from any CNS drugs, other than their neuroleptic, and having

consumed a standard breakfast of plain toast, protein (e.g. cheese, egg, peanut butter) and non-sugared juice. Subjects were then taken into a room where a video camera was set up to record their clinical symptoms (tics) for a total of 15 to 30 minutes. Following this, subjects were ushered into the sound attenuated, electrically shielded, dimly lit, recording chamber where ERP electrodes were attached (~20 to 30 minutes) and a brief practice trial on the computerized attention task was carried out. Following practice, subjects underwent a pre-treatment baseline CPT assessment involving performance/ERP data collection (11.5 minutes). Heart rate and blood pressure were checked prior to the assessment of ERPs and performance on the CPT task.

Pre-treatment assessments were followed by the administration of a transdermal patch (i.e. placebo or nicotine) and a subsequent 4-hour waiting (i.e. drug absorption) interval during which subjects either read preferred material or watched videos. Subjects were also provided with a standardized lunch (a sandwich, saltine crackers and cheese, and non-sugared juice). An adverse symptom checklist (Appendix G) was administered at hourly intervals beginning immediately prior to patch administration, with the final checklist being administered just after the post-placebo/nicotine CPT assessment. When adverse events (e.g. nausea) were found to be clinically significant by the investigators or the study physician, the study was stopped and the subjects were required to stay in the laboratory until the symptoms subsided.

Four hours after the patch administration a second 15-minute videotaping segment and CPT assessment (involving performance and ERP indices), identical to pre-drug assessment, was be carried out. At the end of the test session the transdermal patch was removed.

One week after each of the two acute dose test sessions subjects returned to the laboratory for a follow-up session (10:00 a.m.), including a 15 minute videotaping and computerized ERP-performance task assessment of attention (CPT). No placebo or nicotine patch treatment was given at this time.

Questionnaires related to tics and associated behaviours were completed at the laboratory by the accompanying parent or guardian for the week preceding each acute and follow-up test session.

2.d. Nicotine Dosing

Consistent with previous protocols for this age group (Silver & Sanberg, 1993; Silver et al., 1996), a 7 mg dose of nicotine (titrated to deliver 7 mg over 24 hours) was given to each subject in the form of a transdermal patch. The active nicotine treatment consisted of a Nicoderm® (Marion Merrell Dow) transdermal patch, which was applied to the upper deltoid. In the placebo condition, a transdermal patch with the same physical appearance but containing no centrally active ingredients was applied in the same manner. Both patches (i.e. active and inactive) were then covered with a larger patch. Two subjects discontinued involvement in the study due to vomiting. Given that these two cases of vomiting were with the younger children of small stature, a 5 mg nicotine patch (i.e. Nicotrol®) (Johnson & Johnson-Merck Consumer Pharmaceuticals) was introduced for similarly identified children towards the end of the study in order to minimize the likelihood of adverse events. In total, three children received a 5 mg patch, which delivers 5 mg of nicotine over 16 hours instead of a 7 mg patch, which delivers 7 mg of

nicotine over 24 hours. Twenty subjects received the 7 mg patch. Although all study participants exceeded the minimum weight recommended for use with a 7 mg nicotine transdermal patch by investigators of earlier, similar studies (i.e. 25 kg), it is recommended that any future studies consider beginning nicotine treatment with the smaller dosage (5mg), and once tolerated, titrate up to a higher dose (7, 14 or 21mg). The use of a smaller dosage of nicotine (i.e. 5mg) was made possible by its introduction on the Canadian market during this study. Had it previously been available, it is possible that other researchers may have also used it with the younger children.

2.e. Neuroleptic Treatment

As most of the subjects received twice daily (i.e. b.i.d.) treatment with neuroleptics each morning and evening, all subjects were required to take their morning dose of neuroleptic two hours prior to attending the laboratory test and follow-up sessions. Their TS medication regimens remained constant throughout the study.

2.f. Rating Scales & Questionnaires

a) Tics

1. Tourette Syndrome Symptom List (Revised - TSSL) (Appendix E)

(Leckman, J.F., Towbin, K.E., Ort, S.I. & Cohen, D.J., 1988)

Elicits daily ratings for 7 days (by parents and/or subjects) of a combined rating of number, frequency, and intensity of a broad range of simple and complex motor tics. Vocal tics

are also assessed, although in less detail than motor tics. For ease of administration, both subjects and parents were asked to complete the TSSL on each test day, by estimating averages for each tic category for the previous week. The parent's version is hereafter referred to as TSSL-P. The subjects completed the same inventory with the help of the investigator during the initial 5 minutes of the videotaping session. Their version is hereafter referred to as TSSL-C.

2. Yale Global Tic Severity Scale (YGTSS) (Appendix H)

(Leckman et al., 1989)

A clinical rating instrument that was designed for use in studies of TS and other tic disorders. Used in previous nicotine/neuroleptic TS studies for assessing tic severity in children, adolescents and adults. The YGTSS provides an evaluation of the number, frequency, intensity, complexity, and interference of motor and phonic symptoms. An adapted version of this scale was used in the present study. Estimates were made by the investigator based on information from TSSL-P, TSSL-C, videotaped sessions, and discussions with subjects and their parent or guardian.

b) Associated Behaviour

1. Child Behaviour Checklist (CBCL) (Appendix D)

(Achenbach, 1991)

A reliable and well-recognized parent checklist designed as a standardized tool to provide information about children's adaptive and maladaptive behaviours. Given its length, the CBCL

was completed only once by parents or guardians during the orientation session. As a normed instrument, its usefulness was to provide a baseline profile of the behavioural characteristics of the sample relative to age-matched normal controls.

2. Conners' Parent Rating Scale - Revised: Long Version (Appendix F)

(Conners, 1991)

A second reliable and well-recognized parent checklist in a shorter format than the CBCL, was used in this study to evaluate behavioural changes and treatment efficacy. The Conners was completed by the parent or guardian during each test and follow-up session, providing an estimate of each child's behaviour for the week prior to testing. Unfortunately, the long version was only available in English. French subjects were assessed with the Conners' Parent Questionnaire, for which a translated version was available.

2.g. Videotaping of TS Symptoms

Behavioural assessment of the localization and frequency of tics was determined by videotape, each approximately 15 minutes in duration. Subjects were taken into a room where a video camera was set up to record their clinical symptoms (tics) for a total of 15-30 minutes. The subjects were videotaped for 5 minutes under 3 conditions: a semi-structured interview assessing tics using the TSSL-C (Appendix E) (5 minutes), sitting alone in the room with no instructions (5 minutes) and performing Digit Span and Coding subtests of the Wechsler Intelligence Scale for Children - Third Edition (WISC-III; Wechsler, 1993) with the experimenter (5 minutes). The

variety of videotaping conditions was provided, as the number and type of tic symptoms tend to vary with different stimuli and situations (Shapiro & Shapiro, 1984). For the objective tic assessment, a three-minute segment of the videotaped alone condition was later evaluated for the distribution of motor tics and for the frequency of motor tics and vocalizations by one of the investigators, blind to the treatment conditions. The YGTSS was estimated retrospectively based on a review of the total 15-minute videotaped session, the TSSL-P, TSSL-C, as well as the parent and child's verbal reports of tics for the week prior to each test session. Both Digit Span and Coding were adapted for repeat administration in this study by randomly rearranging numbers and symbols, respectively, to create six different versions.

2.h. Continuous Performance Test Paradigm (CPT)

The CPT, in different presentation styles, has been widely used as a measure of sustained attention. The computerized version used in this study, the Degraded Stimulus - Continuous Performance Task (DS-CPT) (Nestor et al., 1990), has been used in other laboratories to measure sustained attention deficits in schizophrenia as well as the effects of neuroleptics on attention. The advantage of the DS-CPT is that it is perceptually more taxing for encoding processing and is therefore able to pick up more subtle deficits than a perceptually less taxing task. The task required the subjects to detect and respond to rare visual target stimuli and to ignore frequent, nontarget stimuli over an 11.5-minute period. Ten single digits (0-9) were presented in a random sequence (in the centre of the screen) for 100ms at fixed 1100-ms intervals. A stimulus mask remained in the centre of the screen throughout the inter-stimulus interval. Digits were presented

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in the centre of the monitor and subtended to an angle of 0.6° horizontally and 0.9° vertically. Luminance of stimuli was held constant. As with Nestor et al. (1990), the stimuli were degraded such that 30% of the pixels in a 36×40 array were removed from the digit images. Removal was accomplished by reversing the black/white setting of these pixels (Nuechterlein, Edell, Norris & Dawson, 1986). Subjects were seated 1 m from a 14-inch computer monitor on which the CPT stimuli were presented. A total of 486 stimuli were presented at 1200-ms intervals over an 11.5 minute period, and the subjects were instructed to keep their eyes focused on the centre of the monitor, to try to refrain from blinking and to press a mouse key (with the index finger of the dominant hand) only when the designated rare target (0) digit was presented. Subjects were asked to respond as quickly and accurately as possible and told not to respond to the frequent, non-target stimuli. The rare, target digit was presented with a probability of 0.25 resulting in 120 rare targets and 366 frequent, non-targets.

Behavioural performance indices included the proportion of correct responses to target stimuli (i.e. hit rate), response times of correct responses (i.e. reaction time), and the number of behavioural responses to non-target stimuli (i.e. false alarms). Responses were considered correct if they occurred within a 100 to 1100 ms post-rare target time window. Trials with responses outside the 1100 ms time limit were considered misses. Also employed was Grier's signal detection procedure (Grier, 1971) of combining hits and false alarms into non-parametric indices of sensitivity (i.e. *A prime*) and response bias (i.e. *Beta*). The *A prime* is considered a measure of a subject's ability to discriminate a signal from background noise; the higher the *A prime*, the better the processing capacity. The *Beta* is an index of a subject's tendency to over-

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respond or under-respond, and is taken as a measure of responding style. A high *Beta* score reflects a conservative response stance (i.e. sacrificing hits to make fewer errors), and a low *Beta* score reflects a more liberal response stance (i.e. maximizing hits but making more errors). In order to examine the behavioural performance indices for change over time, and to determine whether placebo or nicotine had differential effects as a function of time on task, the data were split into two consecutive 5.75 minute time blocks, each containing 243 stimuli (61 rare targets and 182 frequent, non-targets).

2.i. ERP Recording / Measures

EEG was recorded from three midline scalp sites (FZ, CZ, PZ) using individual tin-plate electrodes, with linked ears as reference. Vertical electro-oculo-graphic (VEOG) activity was recorded with electrodes placed on supra- and infra-orbital ridges of the left eye, while horizontal (HEOG) activity was recorded with electrodes attached to the outer canthi of both eyes. All electrode impedances were kept below 5 kOhms and electrical activity was recorded with bandpass filter settings at 0.1 - 30.0 Hz. Analog-to-digital sampling was carried out on-line at 1.5 ms intervals for a 900 ms sweep duration beginning 100 ms before stimulus onset. Digital data were stored on disc for later off-line ERP processing and analysis. The use of additional electrodes designed to measure muscle artefact was discontinued as they did not provide sufficient additional information to justify their use and were found to be irritating to the subjects to the extent that they potentially interfered with the performance of the task.

Individual sweeps from any site displaying EEG voltages in excess of $\pm 50 \mu\text{v}$ were excluded from further analyses. A minimum of 10 artifact-free, correctly detected rare target stimulus sweeps (per time block) were required to retain a subject's ERP data in the final analysis. Acceptable sweeps, associated with correct responses only, were subjected to eye-movement artifact correction using regression-based weighted coefficients (Semlitsch et al., 1986). Final averages were derived separately to correctly identified targets and non-targets for each of the two 5.75 minute time blocks. Amplitude and latency measures were extracted for each FZ, CZ, and PZ P300, which was defined as the maximum peak positive voltage, in relation to the average pre-stimulus voltage, between 250 and 600 ms post-stimulus. Four P300 area measures were calculated as the sum of voltage values between two latency points relative to pre-stimulus baseline (i.e. Area 1 = 300-375 ms, Area 2 = 375-450 ms, Area 3 = 450-525 ms, Area 4 = 525-600 ms). Grand-averaged P300 waveforms for the first session for all subjects ($N=14$) are shown in Figure 1, with overlapping rare target and frequent, non-target waves at each scalp site (FZ, CZ, PZ) for each time block.

2.j. Statistical Analysis

Statistical analysis was carried out with SPSS (i.e. Statistical Package for Social Sciences) repeated measures analysis of variance (ANOVA). To reduce the occurrence of type I errors resulting from excessive statistical tests, Greenhouse-Geisser corrected p -values were utilized where appropriate and follow-up tests of significant main and interaction effects were

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carried out by simple main effect analysis or pairwise comparison *t*-tests with Bonferroni correction. An alpha level of .05 was used for all statistical tests.

Separate analyses were conducted for acute (i.e. 4 hours post-treatment) and follow-up (i.e. 1 week post-treatment) effects. Within the acute and follow-up data analyses, separate repeated-measures analyses of variance (ANOVA) procedures were applied to each test measure as follows. The only acute clinical measure, tic frequency analysis, was subjected to 2 (tic type: motor and vocal) x 2 (drug: placebo and nicotine) x 2 (time: baseline and 4 hours post-treatment) repeated-measures ANOVA. The acute attentional measures, Digit Span and Coding, were analysed differently, with Digit Span as a 2 (direction) x 2 (drug) x 2 (time), and Coding as a 2 (drug) x 2 (time) repeated-measures ANOVA. The remaining acute attentional measures included the CPT performance and ERP P300 amplitudes, latencies, and areas. For acute effects on the CPT, absolute scores for the five CPT performance measures (reaction time, hits, false alarms, *A prime*, and *Beta*) were analysed by separate 2 (time block: 1 and 2) x 2 (drug) x 2 (time) repeated-measures ANOVAS. For acute effects on ERPs, P300 amplitude and latency values were subjected to separate 3 (site: FZ, CZ, PZ) x 2 (stimulus: rare, frequent) x 2 (block: 1 and 2) x 2 (drug) x 2 (time) repeated-measures ANOVAS. Finally, for acute effects on P300 areas, absolute scores for the four P300 area measures (A1, A2, A3, A4), were analysed by separate 3 (site) x 2 (stimulus) x 2 (block) x 2 (drug) x 2 (time) repeated-measures ANOVAS as well as by combined 4 (area) x 3 (site) x 2 (stimulus) x 2 (block) x 2 (drug) x 2 (time) repeated-measures ANOVAS.

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Clinical follow-up effects of drug administration included: tic frequency (pre- versus 1 week post-treatment), and TSSL-P, TSSL-C, YGTSS and Conners' Parent ratings, comparing tics and behaviour in the week pre-treatment to those in the week post-treatment. Follow-up tic frequency analysis was subjected to 2 (tic type: motor and vocal) x 2 (drug: placebo and nicotine) x 2 (time: pre-treatment baseline and 1 week post-treatment) analysis, while TSSL-P and TSSL-C were analysed with separate 2 (tic type) x 2 (tic complexity: simple and complex) x 2 (drug) x 2 (time) analyses. YGTSS scores were analysed with paired sample *t*-tests, and each Conners index was analysed separately as a 2 (drug) x 2 (time) repeated-measures ANOVA. Follow-up effects on the attentional measures, Digit Span and Coding, were analysed with 2 (direction) x 2 (drug) x 2 (time), and 2 (drug) x 2 (time) repeated-measures ANOVAS, respectively. Follow-up effects on the remaining attentional measures, CPT, ERP amplitudes, latencies, and areas, were analysed in the same way as the acute effects for each measure, except that the acute time factor (time: baseline and 4 hours post-treatment) was replaced with a follow-up time factor (time: baseline and 1 week post-treatment). Follow-up effects on the CPT for each of the five performance measures (reaction time, hits, false alarms, *A prime*, and *Beta*) were analysed by separate 2 (time block: 1 and 2) x 2 (drug) x 2 (time) repeated-measures ANOVAS. Follow-up effects on ERP P300 amplitude and latency values were analysed as separate 3 (site: FZ, CZ, PZ) x 2 (stimulus: rare, frequent) x 2 (block: 1 and 2) x 2 (drug) x 2 (time) ANOVAS. Follow-up effects on the four P300 areas (A1, A2, A3, A4), were analysed by separate 3 (site) x 2 (stimulus) x 2 (block) x 2 (drug) x 2 (time) as well as by combined 4 (area) x 3 (site) x 2 (stimulus) x 2 (block) x 2 (drug) x 2 (time) repeated-measures ANOVAS.

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In addition, attentional measures, including Conners' Parent Rating Scale indices, Child Behavior Checklist - Attention Problems scale, Digit Span, Coding and CPT behavioural performance measures were subjected to bivariate correlational analysis (Pearson product-moment correlation coefficient: Pearson's r , two-tailed tests) in order to examine their inter-relationships.

In order to ensure that the order of treatment administration (i.e. placebo first or nicotine first) did not have an effect on findings, all measures were first subjected to repeated measures ANOVAS, with order included as a between-subjects factor. None of the analyses of potential order effects of treatment presentation showed significant main or order-interaction effects.

3. RESULTS

3.a Adverse Events

Subjects were asked about adverse events immediately before and each hour following the drug challenges. All reported adverse events are listed in Table 2, including those volunteered by subjects (e.g. other: arm pain). The most common complaints were itching at the site of patch application, dizziness, headache and vomiting. The maximum length of time reported for itching at the site of application was 45 minutes. It should be noted that for many of the participants in the present study, no adverse events were reported following nicotine administration, despite a lack of prior exposure to nicotine. Given the lack of acute nicotine challenge effects on tics, it may be that those subjects able to tolerate higher doses of nicotine, may in fact, receive clinical benefits with higher doses. Nevertheless, as previous studies reported clinical effects with 7mg nicotine patches, it was decided to use this standard dose for the majority of nicotine-naïve subjects in the present study.

3.b. Drop Outs

Although initially 23 children and adolescents participated in the study, a total of nine subjects, who engaged in one or more test sessions, were considered dropouts. Two did not complete testing due to adverse events, two did not return for the second drug challenge due to an apparent lack of motivation, one had to be considered a drop out due to technical difficulties resulting in corrupted data, and in four cases, the data was corrupted as a result of actions or inactions on the part of the subjects (e.g. pulling out computer cords or random responding).

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Statistical analysis, for the majority of measures (i.e. tic frequency, YGTSS, CPT performance, ERP P300 amplitudes, latencies and areas), was limited to subjects who had complete data sets (N=14). Given more complete data for Digit Span, Coding, TSSL-P and TSSL-C, data sets for Digit Span and Coding included 16 subjects, while those for TSSL-P and TSSL-C included 18 subjects. Given linguistic inconsistencies of scoring materials for the Conners' Parent Rating Scale, as well as missing attrition data, only 13 subjects were included in the final data set used for analysis.

3.c. **Acute Effects**

3.c.i. **Clinical**

3.c.i.1. *Tic Frequency*

Acute clinical measures, using absolute scores, included motor, vocal and total tic frequency with placebo and nicotine treatment, respectively. No significant drug effects were observed when tic frequency means and standard errors for each of the tic types were compared both within and between treatments (see Table 3). Although vocal tic frequency appeared to increase slightly following placebo (M pre-placebo=1.3; M post-placebo=2.6) and decrease slightly following nicotine (M pre-nicotine=6.1; M post-nicotine=4.4), neither of these approached significance (drug x time: $F(1,13)=.005$, $p=ns$).

3.c.ii. Attentional

3.c.ii.1. Digit Span

Mean ($\pm$ SE) acute absolute scores for Digit Span revealed no significant drug effects.

As shown in Table 4, there was very little change in mean or standard error scores for Digit Span forward, backward, or combined, in either of the treatment conditions.

3.c.ii.2. Coding

Mean ($\pm$ SE) acute absolute scores for Coding revealed no significant drug effects (see Table 5). Although the total number of correct, completed symbols decreased slightly following placebo treatment (M pre-placebo=46.9; M post-placebo=45.3) and increased slightly following nicotine (M pre-nicotine=45.2; M post-nicotine=47.4), the drug x time interaction did not approach significance ($F(1,15)=2.88$, $p=ns$).

3.c.ii.3. CPT Performance

No significant drug effects were noted in any of the five performance measures: reaction time, hit rate, false alarms, *A prime* and *Beta*. Mean and standard error scores for each of the measures in each of the treatment conditions are shown in Table 6. Reaction time (ms) exhibited typical progressive slowing from the first to the second time block in the placebo condition, as one would expect during a sustained attention task (M block 1=410.0; M block 2=448.8). However, no statistically significant differences in reaction time were observed following nicotine treatment relative to placebo. Similar findings were evident for accuracy of responding

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and hit rate (%). While it appears that the decrease in accuracy, for the combined time blocks, was less following nicotine treatment relative to placebo (M pre-placebo=89.1; M post-placebo=81.7 versus M pre-nicotine=86.4; M post-nicotine=83.1), the drug x time interaction did not attain the .05 level of significance ($F(1,13)=1.45$, $p=.25$). More errors of commission (false alarms %) occurred in the post-placebo condition (M pre-placebo=3.7; M post-placebo=5.6), compared to little change in the nicotine condition (M pre-nicotine=4.6; M post-nicotine=4.4), however, again this difference was not significant either within or between groups. *A prime*, a measure of perceptual sensitivity, deteriorated slightly over time in both treatment conditions. *Beta* scores did increase over time within the task except in the post-nicotine condition. While it appeared that nicotine may have prevented the increase in *Beta* (M post-nicotine block 1=.56; M post-nicotine block 2=.53) seen in the pre-nicotine condition (M pre-nicotine block 1=.43; M pre-nicotine block 2=.55) as well as in the pre-and post-placebo conditions, the interaction did not attain the .05 level of significance (block x drug x time: $F(1,13)=.049$, $p=.83$).

3.c.ii.4. CPT ERP - P300 Amplitude & Latency

Means and standard errors for baseline and acute treatment effects on rare and frequent P300 amplitudes and latencies at the three scalp sites (i.e. FZ, CZ, PZ), averaged across the two time blocks, are shown in Tables 7 and 8. The separate and combined time block means and standard errors for PZ P300 amplitudes and latencies, associated with rare and frequent stimuli, are presented in Tables 9 and 10. Grand-averaged acute ERP waveforms are displayed in two separate formats (within treatment and between treatment) at three midline sites in Figure 2.

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P300 amplitudes associated with rare target stimuli were maximal at PZ and minimal at FZ, and all site-specific amplitudes were larger than those associated with frequent stimuli, suggesting that information processing occurred as expected in response to the CPT task. No significant drug effects were observed with P300 amplitudes or latencies. As evidenced by the means in Tables 7 and 8, nicotine did not have the anticipated effect of increasing P300 amplitude nor was there any significant decrease in P300 latency. Although it appears in Figure 2, that nicotine treatment prevented the decrements in P300 amplitudes to rare stimuli seen in the post-placebo acute condition at each of the three scalp sites, this effect was not statistically significant.

3.c.ii.5. CPT ERP: P300 Areas

The P300 area means for rare and frequent stimuli are shown in Tables 11 and 12. No significant drug effects were observed within or between P300 areas in the acute treatment condition. In Figure 2, nicotine appeared to prevent the decrement in the total area of the P300 wave to rare stimuli seen following placebo treatment, an observation that appeared to be supported by a comparison of these same P300 area means for rare stimuli, shown in Table 11. For instance, the decreases in the pre- to post-nicotine summed μv parietal (PZ) area means were between 29% and 87% less than the decreases in the pre- to post-placebo summed μv area means. However, the apparent difference was not supported statistically ($F(2,12)=.137, p=.87$).

3.d. Follow-up Effects

3.d.i. Clinical

3.d.i.1. *Tic Frequency*

No significant drug effects were noted for changes in tic frequency pre- to 1 week post-treatment. Following both treatment conditions, the frequency of total tics decreased (see Table 13), however the drug x time interaction was not significant ($F(1,13)=.025$, $p=.88$), suggesting that neither treatment had any significant impact on total tics, nor on motor or vocal tics (drug x time x tic type: $F(1,13)=1.07$, $p=.32$).

3.d.i.2. *YGTSS*

No significant differences were noted in YGTSS in the weeks preceding and following either placebo or nicotine treatment (see Table 14 for means and standard errors). When individual YGTSS and change scores are compared, improvement in tics following placebo treatment ranged from -11% to 20%, while improvement following nicotine treatment ranged from 3% to 26%, observations that support the role of a placebo effect (see Table 15).

3.d.i.3. *TSSL-P*

No significant drug effects were noted in parent's assessment of weekly averages of tics and associated behaviour in the weeks preceding and following either placebo or nicotine treatment. Parents' symptom ratings were generally higher (see Table 16) than the subjects'

ratings (see Table 17) on all symptoms. Nevertheless, there was very little change evident in parents' mean scores between and within treatment conditions.

3.d.i.4. *TSSL-C*

A significant drug x time x complexity interaction was observed between the subjects' assessments of their tics in the week prior to treatment compared to the week following treatment $F(1,17)=4.788, p=.043$. In the placebo condition, simple tics reportedly decreased significantly following placebo treatment. In the nicotine condition, complex tics reportedly decreased significantly following nicotine treatment (see Table 17).

3.d.i.5. *Conners*

Significant drug x time interactions were noted for four Conners measures (B-Cognitive Problems/Inattention $F(1,12)=5.306, p<.011$; H-Conners ADHD index $F(1,12)=6.358, p<.027$; K-Conners Global Index: Total $F(1,12)=6.088, p<.030$; and N-DSM-IV: Total $F(1,12)=9.128, p<.011$). Comparing pre- and post-treatment T-scores, parent's reported a significant decrease in cognitive problems, related to inattention, after nicotine relative to placebo. Similar decreases in T-scores following nicotine treatment relative to placebo, were reported for ADHD-related behaviour, general problematic behaviour, usually indicative of hyperactivity, and behaviour meeting DSM-IV criteria for combined Inattention and Hyperactive-Impulsive type ADHD (see Table 18).

3.d.ii. Attentional

3.d.ii.1. *Digit Span*

No significant follow-up effects or interactions were observed for scores on Digit Span.

Although as shown in Table 19, the scaled score for the number of digits recalled increased slightly following nicotine treatment relative to placebo for both Digit Span Backwards and Digit Span total, these differences did not reach statistical significance.

3.d.ii.2. *Coding*

A significant drug x time interaction was observed for coding ($F(1,15)=4.973$, $p<.041$), whereby performance on the visuomotor processing task improved significantly following nicotine treatment relative to placebo (see Table 20).

3.d.ii.3. *CPT Performance*

No significant follow-up drug effects were noted in any of the five performance measures: reaction time, hit rate, false alarms, *A prime* and *Beta* (see Table 21 for means and standard errors). Within each measure, the results were consistent with what would be expected with the CPT task paradigm. For instance, hit rate decreased progressively over time in the pre-placebo treatment condition (M block 1=93.1; M block 2=85.1). Although the same decrease occurred in the pre-nicotine condition, nicotine did not prevent the decrement in the post-nicotine condition (M block 1=88.2; M block 2=85.3).

3.d.ii.4. *CPT ERP: P300 Amplitude & Latency*

Means and standard errors for baseline and follow-up treatment effects on rare and frequent P300 amplitudes and latencies at three scalp sites (i.e. FZ, CZ, PZ), averaged across the two time blocks, are shown in Tables 22 and 23. Grand-averaged follow-up ERP waveforms are displayed at the three-midline sites in Figure 3. No significant follow-up drug effects were observed with P300 amplitudes or latencies. However, as shown in Tables 24 and 25, when comparing time blocks within PZ, with rare targets, P300 latency appeared to decrease in the second time block relative to the first following nicotine treatment (M block 1=435.2; M block 2=423.7), while it increased following placebo treatment and in both pre-treatment conditions. While this may have suggested that nicotine decreased stimulus evaluation time or increased the speed of information processing, this difference was not statistically significant.

3.d.ii.5. *CPT ERP: P300 Areas*

No significant drug effects were observed when all four P300 areas were analysed together, nor were drug effects noted with Areas 2 or 3 when they were analysed separately (see Table 26 for means and standard errors for rare stimuli, and Table 27 for frequent stimuli). However, with separate analyses of each of the individual areas, a drug x time interaction $F(1,13)=6.333$, $p<.026$ was noted in Area 1. Following placebo treatment, Area 1 decreased significantly pre- to post-treatment, suggesting that attentional resources were not maintained. The reverse occurred with nicotine treatment, suggesting that nicotine facilitated the maintenance

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of attentional resources (see Figure 3). In addition, post-placebo Area 1 was less than post-nicotine Area 1, although this difference was only marginally significant ($p < .056$).

Finally, a significant site $\times$ stim $\times$ drug $\times$ time interaction $F(2,12)=11.530$, $p < .03$ was observed with Area 4. The results of the pairwise comparisons revealed that, in general, the effects of the task were as expected. Typically, P3 Area 4 differed significantly for rare and frequent stimuli and between the three sites (FZ, CZ, PZ), in the expected directions. In addition, with rare targets at FZ, nicotine and placebo treatment appeared to have inverse effects. With nicotine, Area 4 was negative pre-treatment and increased in negativity post-treatment, while with placebo treatment, P3 Area 4 was negative pre-treatment and became positive thereafter.

3.e. Supplementary Findings

3.e.i. Clinical (subset of subjects taking haloperidol)

When a subset of subjects taking haloperidol ($n=5$) was re-analysed separately, neither acute nor follow-up drug effects on motor or vocal tics were observed (drug $\times$ time $\times$ tic type: $F_{acute}(1,4)=1.02$, $p < .37$; $F_{follow-up}(1,4)=.69$, $p < .45$).

3.e.ii. Correlational Analysis

Pearson's r correlation analysis carried out between Conners' Parent Rating Scale indices and the Child Behavior Checklist (CBCL): Attention Problems scale revealed that the four Conners indices (i.e. Cognitive Problems/Inattentive, Conners' ADHD Index, Conners' Global Index, DSM-IV: Total), which showed significant decreases following nicotine

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treatment relative to placebo, were significantly correlated with one another (ranging from $r=.65$, $p<.03$ to $r=.91$, $p<.001$). None of these indices were significantly correlated with the CBCL: Attention Problems scale (see Table 28). When comparing rating scale attentional indices with other attention measures (see Table 29), the CBCL: Attention Problems scale was positively correlated with Digit Span ($r=.61$, $p<.05$). Digit Span was also positively correlated with the CPT performance measure, *Beta* ($r=.75$, $p<.01$). Of the other CPT attentional performance measures, hit rate and false alarms were inversely related to the perceptual sensitivity index, *A prime* (r hit rate $=.90$, $p<.01$; r false alarms $=-.87$, $p<.01$). Correlational analysis carried out between the above rating scales, attentional measures, and P300 amplitude and latency measures failed to yield any significant relationships between ratings or attentional measures and P300 ERP measures.

4. DISCUSSION

Treatment of children and adolescents with TS is often difficult. In moderate to severe cases, where pharmacological treatment is indicated, neuroleptics are generally the treatment of choice. However, their use is often associated with unpleasant side effects, particularly at higher doses. Research over the past 10 years has investigated the adjunctive use of nicotine with neuroleptics for the potentiation of the reduction of motor symptoms in both animal and human studies. While a variety of delivery systems have been used, transdermal nicotine has been used most recently in conjunction with neuroleptics in individuals with TS. All of the studies conducted thus far in individuals with TS have been case studies or open-blind studies. There have been reports of significant decreases in motor and vocal tics following the application of a single transdermal nicotine patch given in addition to the usual neuroleptic medication. It has been further reported that the decreases in motor activity have lasted for up to 8 weeks, with an average of 1 to 2 weeks. Besides improvements in tic symptomatology, anecdotal reports of improved attention and concentration in TS patients were also noted. This latter observation is of interest given the high co-morbidity of ADHD with TS.

In order to empirically assess the efficacy of this novel treatment, the present study examined the acute and follow-up effects of a nicotine challenge, given in addition to a neuroleptic, on motor activity and attention in children and adolescents with TS and co-morbid ADHD. A double blind, placebo-controlled, crossover design was used as the previous research in this area reported positive clinical and attentional effects resulting from case studies and open blind trials. Objective attentional measures were employed to assess changes in sustained

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attention. In addition to acute assessment, pre- and four hours post-nicotine/placebo, subjects were re-tested on clinical and attentional measures in a follow-up session, one week post-nicotine/placebo. The first goal of the study was to objectively assess acute and follow-up changes in tic symptomatology in a controlled study. The second goal was to assess changes in attention and concentration through a variety of measures, including parents' ratings of behaviour, objective measures of performance, and brain activity during a sustained attention task.

The most significant finding of this study was the lack of either acute (4 hours post-challenge) or follow-up (1 week post-challenge) clinical effects of nicotine, when given adjunctively with a neuroleptic to children and adolescents with TS and co-morbid ADHD. Neither precise (tic counting), nor more general (YGTSS, TSSL-C, TSSL-P) methods of assessing changes in motor and vocal tics yielded evidence of nicotine-mediated change. While parents did report non-specific improvements in attention, as in previous studies, and improvement in performance was noted in a visuomotor task measuring freedom from distractibility, objective measures of sustained attention on a continuous performance test, including behavioural performance and P300 amplitude and latency measures failed to identify any significant effects. While changes in aspects of attention were observed, other than effects on P300 area, no improvements were noted in the ability to sustain attention over time when assessed with objective measures.

4.a. Acute Effects

4.a.i. Clinical

In the present controlled study, 7mg (or 5mg) of transdermal nicotine, given in combination with a neuroleptic, failed to exert any significant acute (i.e. 4 hours post-challenge) effects on the frequency of motor and vocal tics in children and adolescents with TS and co-morbid ADHD. This study attempted to replicate many of the previous sample characteristics by using nicotine-naïve children and adolescents with moderate to severe TS, as per referring physician rating of CGI severity and investigator-established YGTSS ratings. In each case, the severity of the motor and vocal tics was significant enough to require treatment with neuroleptics. As subjects were recruited from a number of referral sources in a given geographical area (Eastern Ontario), prescribing habits differed and as a result two additional neuroleptics (e.g. pimozide and risperidone) were used. This represented a variation from earlier studies, which tended to add nicotine primarily to haloperidol. Nevertheless, both pimozide and risperidone have been reported in the literature as showing clinical efficacy for motor and vocal tic reduction in the treatment of TS (Shapiro & Shapiro, 1984; Shapiro et al., 1989; Lombroso et al., 1995; Bruun & Budman, 1996), suggesting that they share similar dopamine D2 antagonistic properties with haloperidol. Unfortunately, yet perhaps not surprisingly, the study was not able to recruit sufficient subjects with TS alone to establish a separate, comparative sample. The majority of the study participants had TS + ADHD, and as is fairly typical in the TS population, some had additional co-morbid symptoms or diagnoses. As can be concluded by the primary and

secondary medications prescribed, the symptoms most often medicated are those associated with TS or ADHD. As with previous studies, neuroleptic medication regimens were maintained throughout the study, while the pharmacological effects of the shorter-acting stimulants (e.g. dexedrine, methylphenidate), and clonidine were limited by stopping medication on the day of testing.

One of the reasons for this lack of clinical effect in contrast to positive findings in other studies may have been the fact that only 35.7% (n=5) of subjects in the present study were taking haloperidol, while 28.6% (n=4) were taking pimozide, and another 35.7% (n=5) were taking risperidone. However, previous studies reported nicotine-potentiating effects using pimozide as well as haloperidol (Silver, Shytle, Philipp & Sanberg, 1995), and all three neuroleptics used in the present study have dopamine (D2)-blocking properties (Shapiro & Shapiro, 1996; Bruun & Budman, 1996). Even when the subset of subjects taking haloperidol was re-analysed separately, no significant clinical effects were noted. It is important to note that all the subjects met the criteria of insufficient symptom control on haloperidol alone, thus one would expect to see an additional potentiating effect on the remaining tics with the addition of nicotine. On the other hand, reviewing neuroleptic dosing in the TS literature, it appears that the average daily dosage of haloperidol was often, although not always, higher (1mg-8mg) than that in the current sample (.5mg-3mg). Although it appears that the physicians that referred to the current study may have had more conservative prescribing habits, the fact that significant reductions in tics have been reported in drug-naïve TS patients taking nicotine (gum or transdermal) without a neuroleptic suggests that one could have expected to find tic reductions regardless of neuroleptic dosage

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(Dursun et al., 1994; Silver et al., 1996; Dursun & Reveley, 1997). In addition, the early animal studies assessing nicotine's potentiating effect on haloperidol reported significant reductions in movement at even the lowest doses of the neuroleptic (Emerich et al., 1991). Although mg/kg estimates of actual nicotine dosage were not possible in the present study, as body weights were not recorded, the nicotine and neuroleptic doses used in this study may have been significantly lower than those reported in the animal literature. Although the 8-week interval between the two drug challenges, allowing for wash-out of any prolonged nicotine effects, meant that some of the subjects in the current study had one test session during vacation period and one during the potentially more stressful school term, any associated effects were likely counter-balanced by the opposite schedule in other subjects.

The major significant difference between the present study and previous ones is the fact that the present study used a double blind, placebo-controlled, crossover design. The study was specifically designed to test whether the previous reports of nicotine's clinical efficacy as an adjunctive treatment in TS would be empirically validated. The lack of significant clinical findings, despite the variety of measurement tools used, reinforces the importance of rigorous methodology in the assessment of novel treatments. This is particularly important in treatment studies of TS, because of the potential for volitional suppression of tics and phenomenological fluctuations associated with emotional changes and expectations (Goetz et al., 1987).

4.a.ii. Attentional

The research literature upon which this study was based reported improvements in attention and concentration when nicotine was added to a neuroleptic and also when taken alone for the treatment of TS. However, beyond a general reference, the nature of improvements and the type of attention referred to were not clearly identified. With the aim of measuring different aspects of attention and cognitive functioning, a number of different attentional measures were included in this study. The choice of attentional tests was in part based on Mirsky's model of attention which, in turn, was derived from a neuropsychologically based factor analysis of a battery of commonly used tests of attention (Mirsky et al., 1991). The resulting four elements of attention were: encode, focus/execute, sustain, and shift. Representative tests which were suitable for repeat administration included: Digit Span (encode), Coding (focus/execute), and the CPT (sustain). The only test associated with shifting attention was the Wisconsin Card Sorting Test (WCST), which is not suitable for repeat administration, and therefore no tests measuring shifting in attention were included in the present study.

No acute drug effects were observed with either Digit Span, also described as an orally presented index of processing speed, or Coding, a paper and pencil test measuring freedom from distractibility (Sattler, 1992). Children with TS and co-morbid ADHD have previously shown poorer performance on Digit Span relative to those without co-morbid ADHD (Yeates & Bornstein, 1994). Although the current sample of subjects had similar baseline scores on these two tests as those reported above, the lack of current acute nicotine effects may suggest that nicotine does not have an effect on these attentional processes. In support of this supposition,

Digit Span forward, which has previously been used as a measure of working memory and auditory short term memory, as well as attention, was shown to be unaffected by subcutaneous administration of nicotine in both young and elderly healthy normal adult control subjects (Jones et al., 1992). Although non-smokers have shown less susceptibility to distraction when taking nicotine tablets (Wesnes & Warburton, 1978), thus far there have not been any comparative studies using Coding, or the adult version - Digit Symbol, as a measure. Thus, based on the results of only two tests, it did not appear that nicotine administration resulted in an immediate significant improvement in the attentional elements of encoding information or focussing/ executing aspects of attentional tasks.

4.a.ii.1. CPT Performance

No acute drug effects were observed with any of the CPT performance measures, including reaction time, hit rate, false alarms, a prime and beta. The CPT has a long history of research utility as an objective measure of sustained attention (Nestor et al., 1990). The resulting indices can provide useful information about response latency, response styles, perceptual sensitivity, and level of distractibility (Como, 1997). Prior neuropsychological studies with adult TS subjects showed deficits in both sustained and selective attention (Channon et al, 1992). When children with TS were compared with age-matched controls on the CPT, it was found that they had significantly slower reaction times (Shucard et al., 1997). Given the lack of validating measures, such as concurrent electrophysiological sampling, the authors could not conclude whether this finding reflected attentional or motor deficits. They did not find evidence of deficit

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on any other measure of sustained attention obtained from the CPT, nor did they subgroup their sample based on ADHD and OCD co-morbidity. Although nicotine has previously been shown to speed motor responses in smoking and non-smoking normal adults (Heishman et al., 1994), and one would therefore expect that response latency might have decreased following acute administration of nicotine, there was no significant change in reaction time in the present study.

Given ADHD co-morbidity, one would expect that ADHD-associated impairments would be represented in the current sample. In a double blind, placebo-controlled trial of methylphenidate in ADHD adolescents during a CPT test, methylphenidate significantly increased accuracy (e.g. hit rate) and speeded reaction times to targets (Klorman et al., 1991). Through its indirect dopamine agonist properties, nicotine is thought to have similar effects on attention and arousal as psychostimulants, such as methylphenidate (Levin et al., 1996b). Methylphenidate has also been shown to speed reaction time in normal adults (Naylor, Halliday & Callaway, 1985) as has a low dose of subcutaneous nicotine in non-smoking normal adults (Le Houezec, et al., 1994). However, when nicotine was administered transdermally to both smoking and non-smoking adults with ADHD, it was found that nicotine reduced reaction time as well as the variability of responding over the trial blocks in smokers, yet only the variability in response to changing inter-stimulus intervals in non-smoking adults with ADHD (Levin et al., 1996b). Similar to the findings in non-smokers, in the present study, there was no change in reaction time following acute administration with nicotine patches. Variability of responding to changing inter-stimulus intervals was not analysed.

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Given the co-morbidity of ADHD with TS in the current sample, the study expected to find deficits in the ability to sustain attention, which could be “normalized” with nicotine administration. Although it has been reported that TS + ADHD patient groups show a similar pattern of responses on the CPT as those found in ADHD-only populations (Como, 1997), a more recent study comparing children with TS alone, TS plus ADHD, ADHD alone and normal controls, found that while impairment on the CPT was uncommon in the TS alone group, it was common in the ADHD alone and TS plus ADHD groups (Sherman, Shepard, Joschko & Freeman, 1998). More specifically, while all groups performed within normal limits on the measures of reaction time and variability of response latencies, significant impairments on hit rates and false alarms were noted in the TS plus ADHD and ADHD alone groups. From these findings, one would expect that the TS + ADHD subjects in the current study would have impairments on hit rates and false alarms, yet not necessarily on reaction time or variability of reaction time.

It is clear that discrepancies exist in the literature, which make it difficult to predict, as well as interpret attentional findings. Task, as well as patient, variables affect findings. While nicotine has previously been shown to enhance information processing and aspects of sustained attention in normal smokers (Warburton & Walters, 1989; Pritchard, Robinson & Guy, 1992; Warburton & Mancuso, 1998) and non-smokers (Le Houezec et al., 1994; Foulds et al., 1996), as well as in neuropsychiatric populations, including ADHD (Conners et al., 1996; Levin et al., 1996b), Alzheimer’s disease (Sahakian et al., 1989; Jones et al., 1992), and schizophrenia (Levin

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et al., 1996a), nicotine did not evidence cognitive enhancing properties on a sustained attention task in the present study with children and adolescents with TS and co-morbid ADHD.

4.a.ii.2. *CPT ERP: P300*

No significant changes were found in P300 amplitude, latency or area following acute administration of nicotine. These findings were unexpected, given previous reports in the literature of nicotine's effect to speed stimulus evaluation processes as evidenced by a reduction in P300 latency in both smokers (Edwards et al., 1985) and non-smokers (Le Houezec et al., 1994). The current study assessed the effects of nicotine in children and adolescents between the ages of 9 and 17, while previous findings were based on adult samples. The lack of findings in the current study may reflect the differential effects of nicotine on the developmentally immature brains of subjects in this study. Alternatively, given inter-individual variability in nicotine absorption, the optimal therapeutic level of nicotine may not have been achieved. It has previously been reported that nicotine's positive effects on cognitive processing have followed an inverted-U pattern of response (Wesnes & Warburton, 1983), such that effects are not evident with too little or too much nicotine. It is also possible that nicotine does not have significant effects on P300 latency in non-smoking children and adolescents with TS and co-morbid ADHD taking neuroleptics. To date there have been very few studies assessing the effects of nicotine in non-smokers and as previously mentioned, none thus far have studied its effects in children.

Nicotine did not have any significant effect on P300 amplitude or area. This is less surprising given the lack of prior support in the literature for such an effect. However, P300

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amplitudes have consistently been shown to be smaller in children with ADHD and psychostimulants, such as methylphenidate, have been shown to increase P300 amplitudes in the same patient population. Given that nicotine also acts as a stimulant, increasing cortical arousal, it was hypothesized that its' effects might be similar to those of the psychostimulants in children with co-morbid ADHD. In explanation of the lack of convergent findings, it is possible that children with TS and co-morbid ADHD differ fundamentally in the magnitude of their P300 amplitudes from those with ADHD alone. If those with TS and co-morbid ADHD did not have compromised P300 amplitudes to start out with then nicotine may not have any additive or normalizing effect. In this case, the present findings provide support for a recent proposal that there may be subgroups of TS patients that are attentionally intact (Sherman et al., 1998). Further, Halperin et al., (1990) previously proposed that there might be attentive and inattentive subgroups of ADHD patients. It is possible that the co-morbidity of ADHD with TS reflects the attentive type. Nicotine's cognitive enhancing effects have often been shown to be more robust in smokers than non-smokers, where smokers showed greater impairment at baseline (Heishman et al., 1994). In addition, while nicotine has similar properties to the psychostimulants, the effects are not likely to be identical, and therefore nicotine may lack the normalizing effects shown on the P300 amplitudes of children with ADHD treated with methylphenidate.

4.b. Follow-up Effects

4.b.i. Clinical

4.b.i.1. *Tic Symptomatology*

There were no drug effects on motor or vocal tics when the week prior to treatment was compared to the week after treatment. This held true whether the analysis utilized quantitative counts of tic frequency from the videotaped sessions, YGTSS scores or parents' ratings of their children's tics and behaviours (TSSL-P). The only exception to this fairly consistent finding was for the children's own assessment of changes in their tics in the weeks before and after treatment (TSSL-C). They reported a significant decrease in their simple tics following treatment with placebo, and a significant decrease in complex tics following nicotine treatment. Given changes reported in response to both types of treatment, it is possible that increased awareness of tics accounted for the changes rather than changes resulting from nicotine per se. On the other hand, the decrease in complex tics associated with nicotine treatment, may reflect a decrease in the intensity of tics experienced, such that more complex full-body or orchestrated bouts of tics may have been reduced to simple tics. However, there was not a reciprocal increase in simple tics following nicotine treatment.

The lack of follow-up nicotine effects on motor activity was contrary to findings from other studies, which reported that the tic reducing effects of one dose of nicotine could last for up to 8 weeks with an average sustained temporal effect of one to two weeks (Silver et al., 1996). However, all prior reports of prolonged nicotine potentiation of neuroleptics, as well as nicotine effects without concurrent neuroleptics in children and adults with TS were based on case studies

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or open-blind trials, where both investigator's and patient's expectations could have had a significant impact on what was reported. This is particularly true when the YGTSS was used as a measure of change, and the ratings were based on a 50-point scale. In this case, half of the rating (i.e. 25 points) is a subjective report of differential effects in overall improvement from one week to the next. A significant reduction will have a significant impact on overall change, which may reflect the overall estimate of effect rather than specific changes in frequency or intensity per se. In the present study, one of the adolescent subjects spontaneously reported that he noted a significant reduction in his tics that he attributed to wearing what he assumed was the "real"(nicotine) patch. He said that "if (he) could wear a (nicotine) patch every day, (he'd) have no tics". However, when actual tic frequency ratings were compared for the two test sessions on the day in question, baseline total tic frequency was=31 relative to post-treatment total tic frequency=27. Clearly his subjective experience of a significant reduction in tics was much greater than objectively measured. Even if the YGTSS excluded the overall impairment, leaving the total score out of 25 points, an individual's experience of tics could reflect their positive expectations for change or even an actual subjective experience of change in intensity or frequency, for example, without the same magnitude of change being recorded objectively. With a placebo-controlled, double blind trial, a single 7mg dose of nicotine administered in addition to neuroleptics did not result in significant reductions of motor or vocal tics one week after treatment relative to baseline. Given the consistent findings of a lack of change based on a variety of measures, including objective tic frequency ratings, parental, child and investigator subjective ratings, which are in stark contrast to earlier findings reported in the literature, it is

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possible that nicotine's positive potentiating effects on motor and vocal tics in individuals with TS have been overstated or that the effects are limited to those who are taking significantly higher doses of neuroleptics than the subjects in this study. There were two differences in one of the studies reporting prolonged nicotine treatment effects in TS. The investigators used a more selective D2 antagonist, sulpiride, and administered 10 mg nicotine transdermal patches (Dursun & Reveley, 1996). Neither of these agents is available in North America.

4.b.i.2. *Conners*

One of the interesting findings reported in the literature on the nicotine treatment of TS was improved attention and concentration as reported anecdotally by parents. Besides measuring clinical change to the treatment, assessment of changes of attention and concentration was the second major focus of the present study. Again, by using a combination of subjective and objective measures, we aimed to determine the nature, replicability, and validity of such proposed improvements. The Conners' Parent and Teacher Rating scales have long been used to measure behavioural change in clinical trials involving children and adolescents. In the present study, the revised long version of the parent rating scale was chosen to measure a wide variety of behaviours and was administered on each of the four test days. Parents or guardians were asked to assess their child's behaviour for the week preceding each test day thereby providing 1 week pre- and 1 week post-treatment scores on a number of indices. Significant decreases in T-scores were reported on four of 14 indices following nicotine treatment relative to placebo treatment. Significantly less maladaptive behaviour was noted on scales measuring Cognitive

Problems/Inattention, Conners' ADHD Index, Conners Global Index-Total and DSM-IV Total. The Cognitive Problems/Inattention index, describing children as likely to be inattentive, have organizational problems, have difficulty completing tasks, and have problems with concentration, was significantly correlated with the following indices: DSM-IV: Inattentive, Conners ADHD, Conners Global Index: Restlessness-Impulsive, and DSM-IV: Total. Of note is the finding that while parents reported improvement on the Cognitive Problems/Inattention index, significant change was not noted on the DSM-IV: Inattentive index, despite their descriptive similarity as well as the overlap of items associated with the significant correlation ($r=.877$, $p<.0001$). Neither index was significantly correlated with any of the objective behavioural measures of attention (e.g. Digit Span, Coding, CPT performance measures). However, since this significant treatment effect on the Cognitive Problems/Inattention index may be reflecting what was anecdotally reported by parents in previous studies, it is worth considering what is being measured and what is different between this attentional index and the DSM-IV: Inattentive index, which did not show any significant treatment effect. The most likely differentiating themes appear to be related to completing tasks independently and increased ability to concentrate in class. It is possible that these reflect a greater ability to resist distraction rather than the effortful application of attentional resources over time as in a sustained attention task. On the other hand, although the Cognitive Problems/Inattention scale is so named, it does seem to tap a number of attention and non-attention constructs related to schoolwork and completion of activities. While the factor has been named Inattention, the authors may be referring to more general rather than specific aspects of attention.

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The Conners Cognitive Problems/Inattention subscale was significantly correlated with the Child Behavior Checklist (CBCL) scale measuring thought problems ($r=.664$; $p<.026$), yet not the CBCL attention problems scale ($r=.487$; $p<.128$). Clearly the term attention has a variety of interpretations, which is why this study endeavoured to choose empirically supported measures of attention for objective assessment of change. Without any clear change in objective measures, it is difficult to interpret the changes observed in the more general rating scale indices.

Given that significant drug effects were noted on behavioural change as measured by the Conners, it was considered that these may have reflected the effects of risperidone rather than the haloperidol or pimozide, as risperidone is often prescribed for behavioural problems in adolescents. However, when the data was re-analysed to determine whether the significant effects were specific to those who were taking risperidone, it was not found to be so.

While it does seem that non-specific attention changes occurred, the lack of a link to a specific element of attention, may well explain prior anecdotal reports in the literature of improvements in attention and concentration, which included reports of improved ability to complete homework. This study had hypothesized that this may represent improvement in the ability to sustain attention, and yet neither acute nor follow-up performance measure changes supported this.

4.b.ii. Attentional

No drug effects were observed when Digit Span scores one week post-treatment were contrasted with baseline, suggesting that on the basis of this one test, nicotine did not appear to

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facilitate the encoding element of information processing for any prolonged period of time. However, significant improvement was observed in Coding when comparing performance before and one week after treatment with nicotine, relative to placebo. Subjects were able to complete significantly more items in the same amount of time following treatment with nicotine, suggesting a greater ability to focus on the task at hand. This is an interesting finding that may provide more objective support for previous claims of improved concentration observed by parents in children with TS on neuroleptics, who are treated with nicotine. It is also consistent with the significant week-to-week improvement noted on the Conners Cognitive Problems/Inattention scale. The effect appears to be relatively prolonged as it was evident one week after the administration of a single dose of nicotine, however, given that only one test was used to measure the focus/execute element of attention, it would be premature to make any significant claims of benefit without further substantiation. Focussed concentration for a limited period of time seems to have been facilitated, based on a timed, two minute test, however this greater freedom from distractibility may be quite different from the ability to sustain attention over a longer period of time.

4.b.ii.1. CPT Performance

No significant drug effects were noted on any of the CPT behavioural indices when comparing performance at baseline relative to performance one-week post-treatment. This finding suggests that nicotine does not appear to have any facilitatory effects on the vigilance decrement or perceptual sensitivity, in contrast to prior research with nicotine and other

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psychostimulants. Nicotine in non-smoking adults has previously been shown to enhance information processing by decreasing reaction time (Sahakian et al., 1989; Le Houezec et al., 1994), without a speed-accuracy trade off (Foulds et al., 1996). Based on prior findings of increased arousal levels following treatment with psychostimulants, and subsequently improved perceptual sensitivity on the CPT, in children and adolescents with ADHD (Klorman et al., 1991), one would expect that cortical arousal triggered by nicotine might similarly result in improved perceptual sensitivity as evidenced by changes in *A prime* on the CPT. Yet no such changes were noted. Further, given that nicotine has previously been shown to decrease reaction time in both smokers and non-smokers relative to their baseline performance (Heishman et al., 1994), it is interesting to note that no such changes were evident in this study. This may reflect a differential effect of nicotine on children and adolescents relative to adults, or may reflect a counter-balancing effect produced by concurrent neuroleptic treatment. Without comparison with control subjects, it is difficult to know whether baseline levels are impaired. If they are not impaired, then perhaps nicotine has no absolute cognitive-enhancing effects in children or adolescents. There have been limited supportive results of nicotine's cognitive enhancing properties in normal, non-smoking adults, and no previous published studies on the use of nicotine in children, both of which limit the interpretation of the present findings.

4.b.ii.2. CPT ERP: P300

As in the acute condition, no significant drug effects were observed on P300 latency or amplitude. Regarding P300 latency, nicotine has been shown to facilitate the speed of

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information processing through improved stimulus evaluation as evidenced by reductions in P300 latency. This has been one of the most robust findings of nicotine in the electrophysiological literature, and has been demonstrated in both smokers (Edwards et al., 1985; Knott, 1989; Houlihan et al., 1996), and non-smokers (Le Houezec et al., 1994). The lack of such an effect with transdermal nicotine treatment in children and adolescents with TS may be due to immature brain development or may be due to concurrent neuroleptic treatment. As nicotine's electrophysiological effects have not previously been assessed in children and adolescents, the original hypothesis of decreased latency was based on prior findings in adults.

Given the well-documented enhancing effect of the psychostimulants on P300 amplitude in children and adolescents with ADHD (Klorman, 1991), the study hypothesized that nicotine, as a stimulant, might have similar effects. However, before making conclusions about nicotine's lack of effect, it would be important to compare this population of children with TS+ ADHD and normal controls to determine whether the co-morbidity of ADHD differentiates the patients from controls in a fashion similar to those children with ADHD alone, who tend to have smaller P300 amplitudes. If there is no significant difference relative to controls, then there may be no deficit to "normalize" with nicotine. Given that the children of schizophrenic patients also have been shown to have smaller amplitudes on P300s than normal controls, it may be that the psychiatric conditions of ADHD and SZ reflect non-specific, rather than specific, attentional difficulties. Without significant changes in P300 amplitude or latency, it is not possible to conclude that nicotine is having an enhancing effect on either the allocation of attentional resources or on

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improved speed of information processing in children and adolescents with TS and co-morbid ADHD.

When the P300 area was measured, in the follow-up condition, nicotine had significant effects on the first (i.e. 300 - 375 ms) and last (i.e. 525 - 600 ms) quarters of the P300 wave, relative to placebo. Following placebo treatment, the first quarter of the P300 decreased significantly pre- to post-treatment, suggesting that attentional resources were not maintained. The reverse occurred with nicotine treatment, suggesting that nicotine facilitated the maintenance of attentional resources on a sustained attention task. In addition with rare targets, the fourth quarter of the P300 area became more positive following placebo treatment. This did not occur following nicotine, which was negative pre-treatment and increased slightly, but non-significantly in negativity post-treatment. This latter situation in the fourth quarter of the P300 wave was only present frontally, and as greater negativity is typically evident in late waves, it is possible that this post-placebo shift to positivity may reflect altered frontal lobe processing of stimuli due to familiarity of the task or may reflect ocular movements. It may also reflect fatigue or boredom, which is more present in the follow-up rather than the acute session. These changes were not evident with nicotine. In both P300 area situations, while it appears that nicotine may have slightly increased attentional capacity during the sustained attention task, the lack of effect on the total P300 area limits the strength of these findings.

4.c. Acute versus Follow-up Effects

Reviewing both acute and follow-up effects, some tentative conclusions can be made.

When compared to placebo in a double-blind trial, nicotine did not appear to significantly decrease motor or vocal tics in either the acute or follow-up conditions. Absorption of nicotine administered transdermally is considered maximal four hours after administration. Previous studies of open-blind nicotine treatment in TS have reported significant reductions in motor and vocal tics as soon as three hours after transdermal administration of nicotine (Silver et al., 1995), and 15 minutes after patients chewed nicotine gum (Sanberg et al., 1989). In addition, the neuroleptic potentiating clinical effects of a single acute dose of transdermal nicotine have been reported to last for an average of one to two weeks (Silver et al., 1996). However, in contrast to prior reports, the more rigorous methodology of a double blind, placebo-controlled trial failed to provide supportive evidence for either acute or follow-up clinical effects. One difference with the present study, which may in part explain a lack of sustained effects, was that the single dose of transdermal nicotine was applied for only 4 hours relative to 24 hours in previous studies. It may be that chronic nicotine administration inactivates dopamine receptors post-synaptically resulting in prolonged effects. While we would not expect that this time difference in nicotine administration would make any difference to acute, indirect dopamine agonist effects, it may account for a lack of chronic effects.

In contrast to the lack of clinical findings, the present study did reveal nicotine-mediated attentional effects. While no significant acute attentional effects were observed following nicotine administration, there were follow-up effects. Based on the nicotine literature, the study

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had originally hypothesized that nicotine would improve cognitive processing associated with the ability to sustain attention in children and adolescents with TS and co-morbid ADHD. However, the CPT performance results did not support this. Comparing performance prior to nicotine treatment, with performance either one-week later or over the week following nicotine treatment, non-specific improvements in certain aspects of attention were observed. These improvements were noted on the Cognitive Problems/ Inattention subscale of the Conners' Parent Rating Scale, the Coding subtest of the WISC-III, and the area of the P300 in response to target stimuli on the CPT. Interpreting the commonalities of the combination of the positive findings, it appears that nicotine may be enhancing the ability to focus attention for limited periods of time, which in turn facilitates the completion of tasks requiring effortful attention. The distinction between focussed attention for a limited period of time and sustained attention over a longer time period is important and was somewhat unexpected. Given that nicotine has a bi-phasic effect on neurotransmission, initially acting as a dopaminergic agonist, and with sustained receptor binding or inactivation as an antagonist, it may be that we are observing the second phase antagonistic effects in the follow-up findings. Nicotine, administered transdermally, acts as a sustained release delivery system. Although the subjects in this study only received a single acute dose, which was removed four hours after administration, the nicotine interaction with the neuroleptics may well have a potentiating effect of prolonged receptor inactivation. Acute nicotine toxicity in those evidencing significant post-nicotine adverse events may be impairing cognitive performance in the short term, while the nicotine that has successfully bound with receptors, and

resulted in prolonged inactivation of receptors, may be facilitating cognitive performance in the longer term.

4.d. Strengths and Limitations of the Study

The major strength of the present study was the methodology. A double blind, placebo-controlled, crossover design was used as all the previous research in this area reported positive clinical and attentional effects using case studies and open blind trials. In addition, multiple assessment measures, including objective measures, were used to assess changes in tic symptomatology and attention. The subject sample represented a range of moderate to severe TS, typical of those attending both regular and specialized school settings. Finally, the majority of subjects in the present sample were taking relatively low doses of neuroleptics, which reflects current recommended pharmacological treatment strategies for children and adolescents with TS (Kurlan, 1997; Bagheri, Kerbeshian & Burd, 1999).

The study had a number of limiting features, which are related to the following four general categories: technical difficulties associated with the measurement of dependent variables (clinical, behavioural, electrophysiological), manipulation of the independent variable, sample size, and study design and procedure.

A variety of clinical measures were used in order to effectively capture treatment effects on motor activity. Past studies initially used tic frequency rates (McConville et al., 1991) and then, more recently, the YGTSS (Silver et al., 1996). Although both of these measures were used in the present study, given the demands of multiple testing sessions and measuring a number of

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different dependent variables, study-specific adaptations to these may have limited their reliability to detect treatment effects and thus may limit their comparability with previous studies. Tic frequency was recorded during the middle three minutes of a five-minute period of time. Subjects were left alone in the room in order to minimize the need for voluntary tic suppression. The videotape was on for 5 to 10 minutes prior to this, during which time the children were interviewed about their tics, and for a further 5 minutes after during which time they were administered the Digit Span and Coding subtests of the WISC-III. Although the presence of the video camera may have initially intimidated some children, thereby resulting in some initial tic suppression, the general observations of the investigator were that tic frequency and intensity did not differ significantly during the videotaping relative to the other five hours spent with the investigator. On the other hand, leaving the children alone in the room introduced unexpected, if unsurprising, confounding effects. A number of children were reportedly quite anxious and wary about being left alone, even though the investigator was immediately outside the door, while others took the opportunity to misbehave unobserved, resulting in both cases, in difficulty in accurately assessing tic frequency during the given period of time. Nevertheless, the rationale for using this strategy for tic frequency rating was based on prior study recommendations with the same patient population (Shapiro & Shapiro, 1984).

Only one blinded tic rater was used due to limited availability of raters familiar with tic identification, whereas two would have been preferable for verification of reliability of assessment. A three-minute segment of the 5-minute videotaped-alone condition was scored for the distribution of motor tics and for the frequency of motor and vocal tics. Distribution of motor

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tics included the following body areas: eyes, nose, mouth, neck, shoulders, arms, hands, trunk, pelvis, legs, and feet. The frequency score consisted of the number discrete motor tics or vocalizations counted during the three-minute segment. This provided for objective assessment of changes in tics.

The YGTSS, which has previously been used to measure treatment effects of nicotine in similar studies, was adapted for this study, as it was considered inappropriate to be administered with the children alone, a condition which was deemed important in this study to facilitate comfort with the investigator. In addition, given the time commitment associated with the multiple testing sessions used in this study, many parents or guardians were not available to stay with the subjects, often preferring to drop them off at the beginning of the testing day (with the questionnaires already completed) and to pick them up at the end, 6 hours later. As a result, the YGTSS score was extrapolated by the investigator from the tic frequency ratings, the total 20 minute videotaped sessions, the TSSL-C, and the TSSL-P. While this strategy may have compromised comparison with other studies, it was deemed appropriate for the present study. Given the multiple sources of information used to determine this score, including a similar tic inventory reviewed with the subjects in interview format (e.g. the TSSL-C), it is not likely that the YGTSS score would have varied significantly had it been administered in the standard manner.

The final clinical measures, which deserve mention, are the TSSL-P and TSSL-C. The parents' and child's or subject's reports of tic symptom severity for the week preceding each testing session. This measure was chosen to obtain separate, comparable reports of changes in

tics and behaviour. While the inventories were designed to be completed on a daily basis, a weekly average was substituted as it was more appropriate for the children's version, and also because parents often seemed to complete the whole week's inventory just prior to the testing session rather than on a daily basis. Thus for consistency, this inventory was adapted to provide average weekly rather than daily scores.

Finally, reviewing the Conners' Parent's rating scale for behaviour, a decision was made just prior to the beginning of the study to use a longer, more recent version of the scale in order to gain more specific information on any changes in behavioural manifestations of attention. Unfortunately, the longer version was only available in English and as a result, the original translated version administered to the three French subjects was not included in the final analysis. The study design was challenging for the subjects and relatively time consuming for parents and guardians, therefore decisions had to be made to compromise on certain design features, in order to gain as much useful information as possible within the confines of the study resources.

Behavioural measures of attention included the two subtests of the WISC-III, Digit Span and Coding, as well as the CPT. Digit Span and Coding were chosen as they are easily administered tests of processing speed and freedom from distractibility, respectively, and provided a task condition for the videotaping sessions. They were adapted for repeat administration for this study, and as such, the reliability and validity of the adaptations have not been verified. Therefore interpretation and generalizability of the results must be considered in this light. The CPT has a solid reputation as a measure of sustained attention. The CPT-DS (degraded stimulus) version of the test was chosen in order to increase the level of difficulty, and

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thereby avoid potential ceiling effects. The use of the CPT-DS was recommended following prior assessment with the CPT of the same patient population (Shucard et al., 1997).

Nevertheless, without a comparison between subjects with and without co-morbid ADHD, as well as a control group, we cannot be sure that the task adequately differentiates between the groups at baseline. Hypotheses of “normalizing” effects of nicotine are based on the assumptions that the task is sufficiently difficult and that there are significant group differences.

In addition, accurate representation of performance may have been hampered by the subjects' motivation levels as the children were alone in a soundproof room throughout the task. Although they were closely monitored through a video screen in the next room, it was observed that responding styles varied (e.g. random responding, or non-standardized motor responses as a result of shifting the responding hand from dominant to non-dominant), which resulted in the occasional need to discard data from all 6 sessions due to insufficient accurate data in one session. Nevertheless, the response criteria index, *Beta*, did not significantly interact with any other variables in the final data set suggesting that significant confounding variations in motivation were unlikely.

Electrophysiological measures of attention clearly offered the advantage of objective measurement of task-related brain activity. Nevertheless, this particular population of children and adolescents, who displayed excessive movement associated with ADHD symptomatology as well as tics, resulted in artefact that had to be factored out prior to data analysis. While all data sets included in the final analysis contained an acceptable number of epochs (i.e. >10), the quality of the resultant waves may have been compromised somewhat relative to those of other

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patient populations. Although the initial intention was to include two electrodes on the face to record any tic-related artefact, this strategy was abandoned as additional electrodes were found to be too irritating for the subjects.

The second area worth reviewing for potential limitations in the present study, which should be considered when interpreting the results, is related to the manipulation of the two independent variables, nicotine and the neuroleptic used. It is important to consider whether the treatment is of adequate strength to induce measurable treatment effects. As in previous North American studies, a single 7mg dose of nicotine, administered as a transdermal patch, was given to the majority of subjects in the present study. This dosage differed from that used in the UK studies, which have reported on the long-term efficacy of 10mg TNP, given both with and without concurrent neuroleptic treatment (Dursun & Reveley, 1997). However, as perhaps evidenced by the variability in adverse events in the present study, the 7mg dose may have been too high for the smaller, and/or younger children, and on the contrary, may have been too low for the larger adolescents. A 5 mg dose was introduced towards the end of the study for children of smaller stature in order to minimize the incidence of adverse events (e.g. nausea, vomiting). Although this change clearly potentially limits the comparability of this study with others in the literature, it was considered an important adjustment to protocol due to the attrition rate following adverse events of an already limited pool of potential study participants.

Another unanticipated observation was the subjects' apparent ability to differentiate between placebo and treatment patches. Although they appeared visually identical when covered with a larger bandage and were placed so that visual inspection would be difficult (behind the

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right shoulder), the subjects were often able to differentiate between the two, although not always correctly, based on the initial itchiness of the patches containing nicotine. Although the investigators avoided validating any of these suspicions, they could still have had a detrimental effect on reported changes in tics and behaviour.

Finally, while most of the research findings have reported beneficial potentiating effects of nicotine when given in addition to haloperidol, three different neuroleptics were used in this study, haloperidol, pimozide, and risperidone. All have dopamine D2 antagonist properties and have been documented as showing efficacy in the reduction of motor and vocal tics in TS (Shapiro & Shapiro, 1984; Shapiro et al., 1989; Erenberg, 1992; Bruun & Budman, 1996). In addition, pimozide has previously been reported as showing a potentiation effect when given with nicotine in TS patients (Silver et al., 1996). Without a dedicated referral source for this study, it was necessary to rely on a number of different referring physicians for recruitment in order to achieve an adequate sample size. It is also worth mentioning that the neuroleptic doses used by the referring physicians in this study seemed comparatively lower than those reported in the literature upon which this study was based. While this may have potentially reduced treatment effects, there have been reports in the literature of symptomatic improvement in TS patients following nicotine administration in the absence of a neuroleptic (Silver et al., 1996; Dursun & Reveley, 1997).

Finally, one subject in this study was taking 1 mg of benztropine daily to prevent parkinsonian side effects. This dosage was taken on the first test day without the investigator's awareness. When this was discovered, it was decided that for consistency and comparability of

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test days, it would be important for the same medication be taken on the second test day.

However, as this agent has dopamine agonist properties, there may have been a confounding effect when given in conjunction with nicotine.

A third category of factors, which may affect the interpretability of the results, is related to features of the study sample. Presumably given the inclusion and exclusion criteria used, subject recruitment for this study was more difficult than anticipated. Both parents and referring physicians reported some reluctance to the use of neuroleptics as well as reticence about the adjunctive use of an acute dose of nicotine. In the geographical area studied, there were few children or adolescents with TS alone that were severe enough to warrant treatment with neuroleptics. As a result, it was not possible to have a sufficiently large comparative sample of those with TS alone (n=3). Given the high co-morbidity rates associated with TS, many children had co-morbid conditions, which were not necessarily limited to ADHD. Given the potential confounds of additional co-morbid conditions which might affect attention, e.g. obsessive-compulsive disorder, the study initially tried to limit the recruitment to those with TS + ADHD. While theoretically appealing, this did not prove to be as feasible in practice. In order to increase the sample size, certain additional co-morbid conditions were allowed, such as: conduct disorder (n=1), Asperger's syndrome (n=1), obsessive-compulsive symptomatology (n=4), learning disability (n=1) and a sleep disorder (n=1). The study attempted to minimize the effects of any associated pharmacological treatments by ensuring that dosages remained constant throughout the study. In none of the above cases, were the co-morbid conditions or additional medications believed to have a detrimental effect on the ability to complete the study tasks. The ideal study

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design would have included equal sample sizes of those with TS alone and those with TS + ADHD, sex- and age-matched in each sample. However, this goal was further hampered by attrition part way through the study, either following adverse events ($n=2$) or for apparent lack of motivation ($n=3$). Given the crossover design of the study, only those subjects with complete data for all six testing sessions were included in the analysis. As a result, the final sample of subjects with TS only was inadequate ($n=3$), making a comparison of the treatment effects of those with and without ADHD impossible. Of interest is the fact that although these three children did not receive a diagnosis of ADHD from their referring physician, on the inattention subscale of the CBCL, they each received a standard score greater than 1.5 standard deviations above the population norm (i.e. >65), which is a standard that has been used in previous research on ADD (Barkley, 1991). As such, the sample of TS+/-ADHD can be considered relatively homogenous. The final combined sample of TS subjects with and without ADHD was still limited ($n=14$), suggesting the need for replication of the findings using a larger sample. On the other hand, because of the crossover design, the final sample received both treatments and analyses were based on complete data from 6 testing sessions for each subject. Statistical power was considered adequate for this exploratory study. Although it was the first randomized, double-blind, placebo-controlled study assessing adjunctive nicotine's effects on TS tic symptomatology, effect sizes and power calculated for three prior open-blind studies, using nicotine patches or nicotine gum, were effect size₁=.30, power₁=.46 (Silver et al., 1995), effect size₂=.61, power₂=.92 (McConville et al., 1991), and effect size₃=.63, power₃=.997 (Silver et al., 1996). The first two studies used tic frequency counts to measure clinical change, while the third used

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YGTSS. Both of these measures were used in the current study. Given that the current study used a crossover design, further reducing variability, one could have expected a greater effect size than that found in previous studies. However, by selecting an effect size of .50, a sample size of 14 should have provided .80 power with an alpha of .05 for a two-tailed test (Cohen, 1977; Portney & Watkins, 1993). A comparison of groups of TS subjects with and without ADHD, and OCD would complete the study design.

Finally, as with any study design, compromises related to procedural aspects of the study have to be made, which inevitably have their own strengths and weaknesses. A double blind, placebo-controlled, crossover design was chosen for this study as it was considered the most empirically sound design to objectively measure purported treatment effects. Given the prior reports in the literature of neuroleptic potentiating effects of nicotine lasting up to 8 weeks, with an average of one to two weeks, it was important to separate the two treatment testing sessions by the full 8 weeks in order to allow for sufficient washout of any residual treatment effects. It was also decided to include a brief follow-up test session one week after each treatment session in order to assess any follow-up effects. However, the total of 6 testing sessions, two on each treatment day and one a week after each treatment day was quite challenging for many of the subjects. With pre-existing difficulties with attention and impulsivity due to co-morbidity with ADHD, motivation to complete the study requirements was compromised in certain cases, which contributed to the attrition rates. The eight week delay between testing sessions may have limited the comparability of the two treatments given that tics tend to wax and wane over time,

and also given the differential effects on tics of concurrent life circumstances, such as the beginning or ending of the school year, Christmas, and summer holidays.

Despite the above-mentioned limitations of the study, which have an impact on how the results are interpreted, the principles of an empirically driven study were upheld. In contrast to ten years of initial research in the use of nicotine in humans as an adjunctive treatment for the treatment of TS, this is the first double blind, placebo-controlled study using objective measures for assessment of tics and attention.

4.e. Theoretical Implications

Theoretically, the current findings highlight the importance of using double blind, placebo-controlled trials and objective measures to verify the purported efficacy of novel treatments. Although it will be important for the current negative findings concerning adjunctive nicotine to be replicated, this initial controlled study suggests that there does not appear to be any additional clinical benefit provided by nicotine when given with low dose neuroleptics to children and adolescents with TS and co-morbid ADHD. This is the first report of negative effects since the beginning of research in this area. Additional controlled studies using nicotine with higher doses of neuroleptics may reveal different results, as may those examining chronic nicotine dosing using therapeutic levels of nicotine matched to the patient.

Nicotine has demonstrated non-specific improvements in attention and concentration. Nicotine may have prevented some attentional decay seen with placebo on a sustained attention task. However, clearly these findings would have to be replicated prior to making any

substantive conclusions. Although there did not seem to be significant changes in sustained attention, there may have been facilitating effects on the allocation of processing resources on focussed attention tasks of short duration. Given that this observation is based on findings of a few non-specific measures, it will be important to further investigate this possibility with objective measures specifically designed to assess this. Interpretation of electrophysiological baseline comparisons with normal control subjects will also be important to determine the nature of sustained attention abilities in children with TS and ADHD. Given reports in the literature of deficits on the CPT in children with TS and smaller P300 amplitudes in those with ADHD, it was assumed that these variations would both be evident in children with TS, who had co-morbid ADHD, and that nicotine would ameliorate these difficulties. Recent research has proposed that ADHD, when co-morbid with TS, may differ significantly from ADHD alone (Sherman et al., 1998). Extending an earlier finding that there may be both attentive and inattentive subtypes of ADHD alone (Halperin et al., 1990), it is possible that children with TS and co-morbid ADHD do not have deficits in attention per se, rather that they may evidence deficits in the ability to effortfully apply attention skills. Certainly, baseline electrophysiological comparisons with normal controls, particularly with different TS patient subgroups would facilitate interpretation of the current findings. As changes in attention reported in this study were not evident immediately following nicotine administration, they may reflect the secondary dopamine antagonistic effects of prolonged nicotine administration rather than initial agonist effects. As such, chronic rather than acute dosing strategies may be more appropriate to achieve any cognitive enhancing benefit from nicotine. Although they are all psychostimulants, nicotine's

effects on attention may differ significantly from those of methylphenidate or dextroamphetamine. Given that nicotine has been shown to have cognitive enhancing benefits in the treatment of adults with ADHD, it would be interesting to compare the drugs in adolescents with ADHD to determine how their attentional effects differ.

4.f. Clinical Implications

Current findings indicate that adjunctive treatment with nicotine does not appear to significantly reduce tic symptomatology in children and adolescents taking concurrent neuroleptics but does have non-specific effects on behavioural aspects of attention and concentration, particularly for tasks of relatively short duration. Clearly the cost of adverse events associated with the administration of transdermal nicotine needs to be weighed against any potential attentional benefits. Initially it was thought that nicotine treatment in TS might confer benefits on motor activity as well attention and concentration. At this point it is difficult to advocate widespread use of nicotine treatment of TS in children and adolescents given limited and still unclear effects on non-specific attentional processes. Nevertheless, until the current negative findings have been replicated with individuals who are taking higher doses of neuroleptics, there still may be neuroleptic-potentiating benefits on both tics and attention. However, given that current recommendations for the pharmacological treatment of TS emphasize the conservative use of neuroleptics in children and adolescents, and that the current study did not find significant benefit of nicotine in further reducing tics when given with low

dose neuroleptics, nicotine treatment may not be appropriate for the majority of children and adolescents with TS who are taking neuroleptics.

4.g. Suggestions for Future Research

A number of suggestions for future research can be made based on the current research findings. Most important would be the replication of this double blind, placebo-controlled trial of nicotine given adjunctively with neuroleptics in children and adolescents with TS. It would be important to determine whether investigator and subject expectations influenced the previously reported reductions in motor and vocal tics. In the event that such a study was designed, it is recommended that subjects be provided with a minimal dose of nicotine based on weight and/or body mass and this dosage be gradually titrated in order to minimize the occurrence of adverse events. It would also be helpful to compare higher and lower doses of neuroleptics, as earlier findings may have been reflecting dose-related effects. Recent reports in the literature have suggested that mecamylamine, with its cholinergic antagonistic effects which may be similar to nicotine's effects on receptors following chronic or prolonged administration, may effectively reduce tic symptomatology without the adverse events associated with nicotine (Sanberg, Shytle & Silver, 1998). These potential effects would be important to assess in a controlled study. As a cholinergic antagonist, it is not likely that mecamylamine would provide any cognitive enhancing effects.

Regarding attentional effects of nicotine in children and adolescents, there are still conflicting reports in the literature as to the extent, if any, of attentional deficits in children and

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adolescents with TS. Interpretation of the lack of objective improvement in sustained attention with nicotine treatment is hampered by the lack of baseline performance scores. Understanding of attentional as well neuropsychological profiles of children and adolescents with TS is limited given the variability of effects conferred by the co-morbid conditions. Given that the majority of TS patients have co-morbid psychiatric conditions, it would be most beneficial to compare the different subgroups of TS patients using valid objective measures of the different elements of attention as well as a wider spectrum of neuropsychological constructs. Given the tentative follow-up findings with P300, it may be advisable to pursue the use of event-related potentials as non-invasive physiological indices of information processing. Given the reports indicating nicotine may serve to attenuate the influence of task distraction (Knott et al., 1995), special attention may be focussed on the issue of "distractibility", where ERPs might be measured in response to both target events as well as task distractors. An ideal comparison would include the following subgroups: TS alone, ADHD alone, OCD alone, TS + ADHD, TS + OCD, TS + ADHD + OCD, normal controls. Clearly this would be a formidable undertaking, however, without a clear understanding of the differences in attentional and neuropsychological functioning between the groups, it is very difficult to interpret findings of pharmacological agents and make conclusions about their differential effects. It would be important for such a comparison to be conducted with children and adolescents as often faulty assumptions are made based on findings of similar research with cognitively mature adults.

4.h. Conclusions

Besides interfering with the social and academic development of children and adolescents with Tourette syndrome, tic symptomatology can be accompanied by cognitive deficits that may be specific to TS or may be associated with oft-present co-morbid conditions. While treatment with neuroleptics is the treatment of choice in moderate to severe cases of TS, the side effect profile of these drugs, including both physical and cognitive compromise, requires the use of lower doses than those that would completely remove tic symptomatology. Research findings over the past ten years suggesting that nicotine could potentiate the effects of neuroleptics, and therefore further reduce tic symptomatology without using higher doses of neuroleptics, was based on animal studies, case studies and open-blind trials. These findings combined, with additional anecdotal reports of improvements in attention and concentration with the treatment, were very promising, particularly as significant motor and attentional effects were noted with single doses of nicotine and found to last for up to an average of one to two weeks. The nature of the attentional deficits was not clear although the neuropsychological literature on TS initially suggested that children and adolescents with TS showed deficits in sustained attention. Given that many children with TS have co-morbid ADHD, and ADHD has long been theorized to reflect deficits in sustained attention, objective measurement of the ability to sustain attention was warranted. It was hoped that a controlled study would confirm the efficacy of adjunctive nicotine in the treatment of TS. However, the results of an acute dose, double-blind, cross-over study comparing transdermal nicotine and placebo, failed to support the earlier research findings regarding improvements in tic symptomatology. Nor was there much objective support for

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improvements in sustained attention, although there was tentative evidence for an increase in attentional capacity on a sustained attention task with nicotine. Subjects did show improvements in performance on other objective attention tests and parents' rating scales thought to reflect focussed attention on tasks of interest that last a relatively short period of time. While a number of results in the current study point to this possibility, it would be important to specifically set out to measure this differential aspect of attention. In summary, while the current controlled study was an important contribution to the research in this area, it will be important to replicate the lack of clinical findings, particularly with chronic dosing of adjunctive nicotine, and acute dosing of nicotine with higher doses of neuroleptics. In addition, further investigation of any pre-existing attentional deficits in children and adolescents with TS will be important before clear interpretation of nicotine's effects on attention is possible.

Table 1a

Characteristics of the Total Data Sample of Children & Adolescents with Tourette Syndrome (TS) (N=23)

ID, sex, age	Diagnoses	CGI - severity	Neuroleptic (daily total)	Additional medication (daily total)
TS01 (M) 9	TS	moderate-severe	1 mg haloperidol	
TS02 (F) 9	TS, OCS	moderate-severe	1.5 mg haloperidol	
TS03 (M) 9	TS	moderate	1mg pimozide	.175 mg clonidine
TS17 (M) 13	TS, ADHD, OCS, LD, CD	moderate	1mg risperidone	.2 mg clonidine; 10 mg dextedrine
TS18 (M) 10	TS, ADHD, ODD	moderate	2 mg risperidone	10 mg dextedrine
TS19 (M) 13	TS, ADHD	moderate	1 mg risperidone	
TS20 (M) 16	TS, ADHD, OCS	severe	4 mg risperidone	
TS21 (M) 9	TS, ADHD, OCS	moderate	2 mg pimozide	
TS22 (M) 14	TS, ADHD, OCS	moderate-severe	.5 mg haloperidol	
TS23 (F) 11	TS, ADHD	moderate-severe	.5 mg haloperidol	
TS24 (F) 17	TS, ADHD, OCS	moderate	no neuroleptic	
TS25 (M) 8	TS, ADHD	moderate	? mg risperidone	? mg dextedrine
TS26 (M) 12	TS, ADHD	moderate		0.5 mg olanzapine, 0.1 mg clonidine, 20 mg dextedrine
TS27 (M) 13	TS, ADHD	severe	3 mg haloperidol	50 mg methylphenidate; 1 mg benztropine
TS28 (M) 12	TS, ADHD	moderate	.5 mg risperidone	20 mg methylphenidate SR; 20mg methylphenidate PMS; 12.5 mg trazadone
TS29 (M) 17	TS, ADHD, Aspergers	moderate	1.5 mg risperidone	25 mg dextedrine; 20 mg fluoxetine
TS30 (M) 8	TS, ADHD, OCS, LD	severe	0.75 mg risperidone	0.3 mg clonidine, 15 mg dextedrine

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TS31(M) 13	TS, ADHD	moderate	1.5 mg risperidone	40 mg methylphenidate
TS32 (M) 9	TS, ADHD	moderate	0.5 mg risperidone	30 mg methylphenidate 0.25 mg clonidine
TS33 (M) 14	TS, ADHD	moderate-severe	4 mg pimozide	.2 mg clonidine; 20 mg dexedrine; 10mg paroxetine
TS34 (M) 14	TS, ADHD	moderate-severe	1mg pimozide	.25 mg clonidine; 60 mg methylphenidate
TS35 (F) 14	TS, ADHD	moderate	1 mg risperidone	150 mg bupropion
TS36 (M) 9	TS, ADHD	moderate-severe	1 mg pimozide	.5 mg risperidone

ADHD= Attention Deficit (Hyperactivity) Disorder
LD= Learning disabilities
ODD=Oppositional Defiant Disorder

OCS= Obsessive-compulsive symptomatology
CD= Conduct Disorder
?= Dosage unknown

Table 1b

Characteristics of the Final Data Sample of Children & Adolescents with Tourette Syndrome (TS) (N=14)

ID, sex, age	Diagnoses	CGI - severity	YGTSS baseline	Neuroleptic (daily total)	Additional medication (daily total)
TS01 (M) 9	TS	moderate-severe	65	1 mg haloperidol	
TS02 (F) 9	TS, OCS	moderate-severe	66	1.5 mg haloperidol	
TS03 (M) 9	TS	moderate	45	1 mg pimozide	.175 mg clonidine
TS17 (M) 13	TS, ADHD, OCS, LD, CD	moderate	53	1 mg risperidone	.2 mg clonidine; 10 mg dexedrine
TS20 (M) 16	TS, ADHD, OCS	severe	83	4 mg risperidone	
TS22 (M) 14	TS, ADHD, OCS	moderate-severe	66	.5 mg haloperidol	
TS23 (F) 11	TS, ADHD	moderate-severe	63	.5 mg haloperidol	
TS27 (M) 13	TS, ADHD	severe	81	3 mg haloperidol	50 mg methylphenidate; 1 mg benztrapine
TS28 (M) 12	TS, ADHD	moderate	54	.5 mg risperidone	20mg methylphenidate SR; 20mg methylphenidate PMS 12.5 mg trazadone
TS29 (M) 17	TS, ADHD, Aspergers	moderate	36	1.5 mg risperidone	25 mg dexedrine; 20 mg fluoxetine
TS31(M) 13	TS, ADHD	moderate	38	1.5 mg risperidone	40 mg methylphenidate PMS
TS33 (M) 14	TS, ADHD	moderate-severe	54	4 mg pimozide	.2 mg clonidine; 20 mg dexedrine; 10mg paroxetine
TS34 (M) 14	TS, ADHD	moderate-severe	48	1mg pimozide	.25 mg clonidine; 60 mg methylphenidate SR
TS36 (M) 9	TS, ADHD	moderate-severe	49	1 mg pimozide	.5 mg risperidone

ADHD= Attention Deficit (Hyperactivity) Disorder
LD= Learning disabilities

OCS= Obsessive-compulsive symptomatology
CD= Conduct Disorder

Table 2

Adverse Events Reported Following Nicotine and Placebo Treatment

Adverse Event	#CN	%CN	#CP	%CP	#DN	%DN	#DP	%DP
dizziness	4/14	28.6	2/14	14.3	4/9	44.0		
weak/faint	1/14	7.1			3/9	33.0	1/9	11.0
headache	2/14	14.3	2/14	14.3	1/9	11.0	1/9	11.0
ringing in ears								
palpitations								
nausea	1/14	7.1	1/14	7.1	2/9	22.0		
cramps					2/9	22.0	1/9	11.0
chest pain					1/9	11.0		
breathing difficulties								
numbness	1/14	7.1						
vomiting	2/14	14.3			3/9	33.0		
itching at site	8/14	57.1	2/14	14.3	3/9	33.0	1/9	11.0
other (arm pain)			1/14	7.1				

CN= Completers, following nicotine challenge

CP= Completers, following placebo challenge

Completers = 14 subjects included in final analysis, for whom complete data was available for both nicotine (CN) and placebo (CP) challenges.

DN= Drop-outs, following nicotine challenge

DP= Drop-outs, following placebo challenge

Dropouts = 9 subjects who were considered dropouts as complete data was not available.

Table 3

Clinical Mean (+/-SE) Scores: Pre- versus Acute (4 hours) Post-treatment Effects on
Motor, Vocal and Total Tic Frequencies (N=14)

	Placebo				Nicotine			
	Pre		Post		Pre		Post	
Tic type	M	(SE)	M	(SE)	M	(SE)	M	(SE)
Motor	17.1	(2.9)	13.4	(2.7)	17.1	(2.5)	16.8	(3.2)
Vocal	1.3	(0.6)	2.6	(0.9)	6.1	(2.2)	4.4	(2.3)
Total	18.4	(3.0)	16.0	(2.3)	23.3	(3.7)	21.1	(4.6)

Table 4

Clinical Mean (+/-SE) Scores: Pre- versus Acute (4 hours) Post-treatment Effects on

Digit Span Forwards, Digit Span Backwards, and Digit Span Total (N=16)

	Placebo				Nicotine			
	Pre		Post		Pre		Post	
	M	(SE)	M	(SE)	M	(SE)	M	(SE)
Digit Span - Forward	7.9	(0.4)	8.1	(0.4)	7.4	(0.4)	7.9	(0.4)
Digit Span - Backward	4.7	(0.3)	4.3	(0.3)	4.6	(0.3)	4.7	(0.3)
Digit Span - Total	12.6	(0.5)	12.4	(0.6)	11.9	(0.5)	12.6	(0.5)

Table 5

Clinical Mean (+/-SE) Scores: Pre- versus Acute (4 hours) Post-treatment Effects on

Coding (N=16)

	Placebo				Nicotine			
	Pre		Post		Pre		Post	
	M	(SE)	M	(SE)	M	(SE)	M	(SE)
Coding	46.9	(3.1)	45.3	(2.8)	45.2	(2.8)	47.4	(3.1)

Table 6

CPT Mean (+/-SE) Performance Scores: Pre- versus Acute (4 hours) Post-treatmentEffects on Reaction Time (ms), Hit Rate (&), False Alarms (%), *A Prime*, and *Beta* for TwoSeparate and Combined Time Blocks (N=14)

	Placebo				Nicotine			
	Pre		Post		Pre		Post	
Reaction Time (ms)	M	(SE)	M	(SE)	M	(SE)	M	(SE)
Block 1	410.0	(16.9)	435.9	(21.9)	425.4	(16.7)	442.7	(14.3)
Block2	448.8	(17.5)	470.6	(20.9)	475.7	(12.7)	481.9	(17.3)
Combined	429.1	(16.8)	453.8	(20.7)	450.7	(14.1)	461.9	(15.0)
Hit Rate (%)	M	(SE)	M	(SE)	M	(SE)	M	(SE)
Block 1	93.1	(2.0)	86.1	(3.6)	89.9	(2.0)	86.7	(3.6)
Block2	85.1	(3.4)	77.2	(4.9)	83.1	(2.7)	79.7	(4.6)
Combined	89.1	(2.6)	81.7	(4.1)	86.4	(1.9)	83.1	(3.8)
False Alarms (%)	M	(SE)	M	(SE)	M	(SE)	M	(SE)
Block 1	3.5	(1.1)	5.1	(1.9)	4.1	(1.2)	3.8	(1.0)
Block2	4.1	(1.4)	6.3	(2.2)	5.3	(1.8)	5.2	(1.6)
Combined	3.7	(1.2)	5.6	(2.0)	4.6	(1.5)	4.4	(1.2)
<i>A prime</i>	M	(SE)	M	(SE)	M	(SE)	M	(SE)
Block 1	0.97	(0.00)	0.94	(0.02)	0.96	(0.00)	0.95	(0.01)
Block2	0.95	(0.01)	0.91	(0.03)	0.94	(0.01)	0.93	(0.02)
Combined	0.96	(0.01)	0.93	(0.02)	0.95	(0.00)	0.94	(0.02)

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<i>Beta</i>	M	(SE)	M	(SE)	M	(SE)	M	(SE)
Block 1	0.28	(0.10)	0.46	(0.07)	0.43	(0.09)	0.56	(0.07)
Block2	0.48	(0.07)	0.56	(0.07)	0.55	(0.07)	0.53	(0.10)
Combined	0.42	(0.07)	0.54	(0.07)	0.52	(0.07)	0.58	(0.09)

Table 7

CPT ERPs: Pre- versus Acute (4 hours) Post-treatment Effects, Averaged Across the Two Time Blocks, on Rare and Frequent P300 Amplitudes (μV) at 3 (FZ,CZ,PZ) Scalp Sites (N=14)

Rare	Placebo				Nicotine			
	Pre		Post		Pre		Post	
scalp site	M	(SE)	M	(SE)	M	(SE)	M	(SE)
FZ	3.3	(1.0)	1.1	(1.0)	4.0	(1.3)	3.8	(1.2)
CZ	10.9	(1.5)	6.9	(1.4)	9.5	(1.3)	7.9	(1.3)
PZ	14.4	(1.3)	10.5	(1.6)	13.1	(1.2)	11.0	(0.9)
Frequent								
scalp site	M	(SE)	M	(SE)	M	(SE)	M	(SE)
FZ	2.3	(0.6)	2.7	(0.7)	3.1	(0.7)	2.9	(0.7)
CZ	5.3	(0.6)	5.0	(1.0)	5.5	(0.6)	4.9	(0.9)
PZ	5.8	(0.5)	5.2	(0.9)	5.5	(0.8)	4.5	(0.8)

Table 8

CPT ERPs: Pre- versus Acute (4 hours) Post-treatment Effects, Averaged Across the Two Time Blocks, on Rare and Frequent P300 Latencies (ms) at 3 (FZ,CZ,PZ) Scalp Sites (N=14)

Rare	Placebo				Nicotine			
	Pre		Post		Pre		Post	
scalp site	M	(SE)	M	(SE)	M	(SE)	M	(SE)
FZ	410.3	(26.6)	396.8	(23.2)	441.8	(21.2)	438.8	(23.3)
CZ	437.4	(19.7)	454.9	(26.6)	437.8	(16.4)	445.5	(19.6)
PZ	452.3	(14.4)	428.0	(20.4)	449.6	(10.2)	459.7	(12.9)
Frequent								
scalp site	M	(SE)	M	(SE)	M	(SE)	M	(SE)
FZ	411.4	(21.7)	415.9	(27.6)	440.3	(22.7)	416.7	(28.2)
CZ	413.3	(20.4)	445.4	(31.0)	473.7	(24.0)	422.0	(26.1)
PZ	497.4	(25.1)	465.3	(31.2)	492.7	(21.4)	483.9	(29.8)

Table 9

CPT ERPs: Mean (+/-SE) Scores Pre- versus Acute (4 hours) Post-treatment Effects on Rare and Frequent P300 Amplitudes (μV) at PZ Scalp Site, with Respect to Separate and Combined Time Blocks (N=14)

	Placebo				Nicotine			
	Pre		Post		Pre		Post	
Rare								
PZ	M	(SE)	M	(SE)	M	(SE)	M	(SE)
Block 1	16.3	(1.8)	10.9	(1.6)	13.7	(1.3)	12.6	(1.3)
Block 2	14.1	(0.9)	12.0	(1.1)	13.1	(1.6)	10.7	(1.2)
Combined	14.4	(1.3)	10.5	(1.6)	13.1	(1.2)	11.0	(0.9)
Frequent								
PZ	M	(SE)	M	(SE)	M	(SE)	M	(SE)
Block 1	6.2	(0.7)	5.1	(0.8)	5.5	(0.9)	4.9	(1.0)
Block 2	5.8	(0.5)	5.7	(1.1)	6.3	(0.9)	4.7	(0.7)
Combined	5.8	(0.5)	5.2	(0.9)	5.6	(0.8)	4.5	(0.8)

Table 10

CPT ERPs: Mean (+/-SE) Scores Pre- versus Acute (4 hours) Post-treatment Effects on Rare and Frequent P300 Latencies (ms) at PZ Scalp Site, with Respect to Separate and Combined Time Blocks (N=14)

	Placebo				Nicotine			
	Pre		Post		Pre		Post	
Rare								
PZ	M	(SE)	M	(SE)	M	(SE)	M	(SE)
Block 1	452.5	(13.5)	426.0	(14.9)	442.5	(9.6)	446.2	(12.9)
Block 2	455.4	(19.5)	433.9	(24.8)	456.8	(11.8)	488.3	(20.0)
Combined	452.3	(14.5)	428.0	(20.4)	449.6	(10.2)	459.7	(12.9)
Frequent								
PZ	M	(SE)	M	(SE)	M	(SE)	M	(SE)
Block 1	455.6	(26.9)	485.7	(30.0)	490.7	(21.9)	509.4	(29.2)
Block 2	509.1	(23.9)	468.1	(34.5)	512.5	(27.5)	461.1	(28.5)
Combined	497.4	(25.1)	465.4	(31.3)	492.7	(21.4)	483.9	(29.8)

Table 11

CPT ERPs: Pre- versus Acute (4 hours) Post-treatment Effects on Four P300 Area (summed μV)**Means (+/- SE) at 3 (FZ, CZ, PZ) Scalp Sites for Rare Stimuli, Averaged Across the Two Time****Blocks (N=14)**

	Placebo				Nicotine			
	Pre		Post		Pre		Post	
FZ (summed μV)	M	(SE)	M	(SE)	M	(SE)	M	(SE)
Area 1	-39.3	(29.7)	-93.1	(40.4)	-23.6	(48.6)	-30.2	(41.1)
Area 2	-18.2	(45.8)	-108.0	(52.4)	10.4	(61.3)	12.4	(59.7)
Area 3	-67.6	(46.7)	-132.8	(50.0)	20.8	(47.1)	-4.3	(49.2)
Area 4	-85.9	(48.4)	-138.4	(42.5)	-16.6	(45.2)	-34.0	(47.9)
CZ (summed μV)	M	(SE)	M	(SE)	M	(SE)	M	(SE)
Area 1	201.9	(54.3)	103.1	(53.7)	142.2	(52.8)	93.3	(41.6)
Area 2	313.3	(72.7)	152.1	(61.3)	240.0	(65.1)	184.4	(60.6)
Area 3	259.6	(60.4)	129.8	(55.1)	245.0	(52.1)	181.6	(52.8)
Area 4	217.5	(65.2)	126.9	(54.2)	192.2	(44.7)	134.2	(48.8)
PZ (summed μV)	M	(SE)	M	(SE)	M	(SE)	M	(SE)
Area 1	326.6	(56.3)	221.0	(64.6)	227.4	(50.1)	182.1	(31.8)
Area 2	499.3	(57.0)	320.6	(66.9)	395.5	(58.9)	343.0	(44.4)
Area 3	457.6	(44.0)	305.0	(50.4)	407.8	(42.0)	321.0	(35.6)
Area 4	367.0	(42.7)	228.5	(49.6)	306.1	(36.3)	247.4	(31.1)

Note: Area 1 = 300-375 ms
Area 2 = 375-450 ms

Area 3 = 450-525 ms
Area 4 = 525-600 ms

Table 12

CPT ERPs: Pre- versus Acute (4 hours) Post-treatment Effects on Four P300 Area (summed μV)

Means (+/- SE) at 3 (FZ, CZ, PZ) Scalp Sites for Frequent Stimuli, Averaged Across the Two

Time Blocks (N=14)

	Placebo				Nicotine			
	Pre		Post		Pre		Post	
FZ (summed μV)	M	(SE)	M	(SE)	M	(SE)	M	(SE)
Area 1	-37.3	(15.1)	9.1	(21.2)	-24.6	(18.8)	24.4	(22.0)
Area 2	13.3	(32.8)	8.8	(36.7)	21.4	(23.9)	26.9	(38.9)
Area 3	-42.6	(32.2)	-33.0	(42.1)	0.5	(35.3)	5.5	(39.1)
Area 4	-64.2	(29.9)	-16.4	(33.9)	-26.4	(24.3)	-3.2	(29.8)
CZ (summed μV)	M	(SE)	M	(SE)	M	(SE)	M	(SE)
Area 1	67.7	(18.8)	77.1	(32.4)	51.3	(22.9)	98.7	(24.9)
Area 2	131.1	(33.9)	89.5	(50.5)	118.6	(30.2)	118.9	(48.1)
Area 3	85.5	(39.6)	64.7	(55.4)	107.6	(31.4)	94.8	(45.5)
Area 4	74.1	(35.4)	99.1	(46.8)	92.9	(22.4)	98.1	(38.7)
PZ (summed μV)	M	(SE)	M	(SE)	M	(SE)	M	(SE)
Area 1	81.3	(21.9)	79.4	(28.1)	46.6	(27.0)	46.8	(21.3)
Area 2	153.1	(23.1)	104.4	(42.6)	131.9	(28.8)	96.1	(33.2)
Area 3	111.9	(32.2)	72.3	(50.2)	109.3	(32.5)	65.2	(34.9)
Area 4	97.5	(34.9)	108.3	(44.0)	96.1	(32.6)	88.0	(33.4)

Note: Area 1 = 300-375 ms
Area 2 = 375-450 ms

Area 3 = 450-525 ms
Area 4 = 525-600 ms

Table 13

Clinical Mean (+/-se) Scores: Pre- versus Follow-up (1 week) Post-treatment Effects on Motor,Vocal and Total Tic Frequencies (N=14)

Tic type	Placebo				Nicotine			
	Pre		Post		Pre		Post	
	M	(SE)	M	(SE)	M	(SE)	M	(SE)
Motor	17.1	(2.9)	12.8	(2.8)	17.1	(2.5)	15.9	(3.3)
Vocal	1.3	(0.6)	2.1	(1.1)	6.1	(2.2)	4.5	(2.1)
Total	18.4	(3.0)	14.9	(3.1)	23.3	(3.7)	20.4	(3.4)

Table 14

Clinical Mean (+/-SE) Scores: 1 Week Pre- versus 1 Week Post-treatment Effects on Yale GlobalTic Severity Scale (YGTSS) (N=14)

Symptom	Placebo				Nicotine			
	Pre		Post		Pre		Post	
	M	(SE)	M	(SE)	M	(SE)	M	(SE)
Total motor tic score/25	14.2	(1.1)	12.6	(1.5)	14.3	(1.3)	13.1	(1.1)
Total phonic tic score/25	13.6	(0.9)	12.7	(1.0)	13.8	(1.0)	12.5	(1.1)
Total tic score/50	27.9	(2.1)	25.3	(2.3)	28.7	(2.5)	25.7	(2.0)
Overall Impairment Rating/50	28.5	(2.0)	28.5	(2.0)	29.3	(2.2)	27.8	(1.9)
Global Severity Score/100	56.4	(3.6)	53.8	(3.8)	58.0	(4.3)	53.4	(3.4)

Table 15

Individual YGTSS and Change Scores: 1 Week Pre- versus 1 Week Post-treatment Effects onYale Global Tic Severity Scale (YGTSS) (N=14)

Patient ID	Placebo			Nicotine		
	Pre-YGTSS	Post-YGTSS	% Change	Pre-YGTSS	Post-YGTSS	% Change
TS01	61	58	5	65	58	11
TS02	66	59	11	84	62	26
TS03	45	38	16	43	38	12
TS17	53	53	0	53	50	6
TS20	81	81	0	83	65	22
TS22	60	60	0	66	66	0
TS23	63	58	8	63	61	3
TS27	81	81	0	80	80	0
TS28	54	43	20	54	54	0
TS29	36	35	3	35	35	0
TS31	38	42	-11	38	38	0
TS33	54	52	4	56	53	5
TS34	48	48	0	48	48	0
TS36	49	45	8	44	42	5

Table 16

Clinical Mean (+/-SE) Scores: 1 Week Pre- versus 1 Week Post-treatment Effects on Tourette**Syndrome Symptom List - Parent's Report (TSSL-P) (N=18)**

	Placebo				Nicotine			
	Pre		Post		Pre		Post	
Symptom	M	(SE)	M	(SE)	M	(SE)	M	(SE)
Simple motor	13.4	(2.5)	11.7	(2.5)	11.5	(2.9)	10.4	(2.1)
Complex motor	12.3	(2.7)	12.7	(2.9)	12.7	(2.6)	11.7	(2.2)
Simple vocal	7.9	(1.6)	7.3	(1.7)	7.8	(1.6)	5.8	(1.1)
Complex vocal	8.2	(1.8)	8.1	(1.8)	7.1	(1.1)	6.3	(1.1)
Behavior	11.0	(1.5)	11.4	(1.7)	11.0	(1.3)	10.0	(1.4)
Total	41.9	(8.0)	39.8	(8.4)	39.2	(7.6)	34.2	(5.8)

Table 17

Clinical Mean (+/-SE) Scores: 1 Week Pre- versus 1 Week Post-treatment Effects on Tourette

Syndrome Symptom List - Child's Report (TSSL-C) (N=18)

	Placebo				Nicotine			
	Pre		Post		Pre		Post	
Symptom	M	(SE)	M	(SE)	M	(SE)	M	(SE)
Simple motor	9.1	(1.3)	6.8	(1.3)	9.8	(1.7)	7.9	(1.8)
Complex motor	6.9	(1.6)	3.9	(1.0)	8.6	(2.0)	5.1	(1.0)
Simple vocal	3.7	(0.9)	1.7	(0.4)	3.8	(1.0)	3.7	(1.0)
Complex vocal	3.6	(1.1)	3.3	(0.9)	3.9	(1.0)	2.8	(0.8)
Behavior	6.3	(1.3)	3.5	(0.7)	5.9	(1.0)	4.6	(1.1)
Total	23.3	(4.3)	15.7	(2.6)	25.7	(4.1)	19.5	(3.7)

Table 18

Clinical Mean (+/-SE) Scores: 1 Week Pre- versus 1 Week Post-treatment Effects on Conners'**Parent Rating Scale Indices (T-scores) (N=13)**

		Placebo				Nicotine			
		Pre		Post		Pre		Post	
	Index	M	(SE)	M	(SE)	M	(SE)	M	(SE)
A	Oppositional	73.5	(4.9)	73.1	(4.5)	74.1	(4.2)	69.2	(4.3)
B	Cognitive Problems/ Inattentive	66.7	(2.9)	67.0	(2.4)	68.0	(2.5)	62.7	(2.6)*
C	Hyperactivity	76.5	(4.6)	76.6	(5.1)	76.9	(4.9)	72.4	(5.1)
D	Anxious-Shy	75.2	(5.4)	68.7	(5.0)	71.2	(5.8)	67.2	(5.0)
E	Perfectionism	57.5	(4.0)	55.8	(3.2)	55.4	(3.5)	54.5	(3.4)
F	Social Problems	73.8	(4.9)	71.0	(3.5)	73.2	(4.8)	69.6	(4.7)
G	Psychosomatic	67.2	(5.6)	61.4	(4.8)	67.6	(5.5)	60.2	(5.2)
H	Conners ADHD Index	71.2	(2.3)	70.2	(2.2)	72.3	(2.9)	66.1	(2.4)*
I	CGI: Restlessness	74.5	(3.1)	74.6	(6.4)	70.1	(3.6)	70.2	(3.6)
J	CGI: Emotional Lability	70.4	(4.8)	71.8	(4.4)	72.6	(5.0)	66.9	(4.6)
K	CGI: Total	75.0	(3.7)	76.3	(4.0)	75.1	(4.0)	70.4	(3.9)*
L	DSM-IV: Inattentive	69.8	(2.7)	70.2	(2.4)	69.2	(2.9)	65.8	(2.4)
M	DSM-IV: Hyperactive/ Impulsive	76.5	(4.0)	76.6	(4.5)	77.5	(4.5)	69.7	(4.0)
N	DSM-IV: Total	74.2	(3.1)	75.7	(3.5)	75.0	(3.7)	69.0	(2.9)*

* significant drug x time interaction at the .05 level

Table 19

Clinical Mean (+/-SE) Scores: Pre- versus Follow-up (1 week) Post-treatment Effects on Digit Span Forwards, Digit Span Backwards, and Digit Span Total (N=16)

	Placebo				Nicotine			
	Pre		Post		Pre		Post	
	M	(SE)	M	(SE)	M	(SE)	M	(SE)
Digit Span - Forward	7.9	(0.4)	8.3	(0.3)	7.4	(0.4)	8.0	(0.5)
Digit Span - Backward	4.7	(0.3)	4.4	(0.4)	4.6	(0.3)	5.1	(0.3)
Digit Span - Total	12.6	(0.5)	12.7	(0.6)	11.9	(0.5)	13.1	(0.7)

Table 20

Clinical Mean (+/-SE) Scores: Pre- versus Follow-up (1 week) Post-treatment Effects on Coding (N=16)

	Placebo				Nicotine			
	Pre		Post		Pre		Post	
	M	(SE)	M	(SE)	M	(SE)	M	(SE)
Coding	46.9	(3.1)	48.0	(3.4)	45.2	(2.8)	51.3	(2.7)

Table 21

CPT Mean (+/-SE) Performance Scores: Pre- versus Follow-up (1 week) Post-treatment Effects on Reaction Time (ms), Hit Rate (%), False Alarms (%), *A Prime*, and *Beta* for Two Separate and Combined Time Blocks (N=14)

	Placebo				Nicotine			
	Pre		Post		Pre		Post	
Reaction Time (ms)	M	(SE)	M	(SE)	M	(SE)	M	(SE)
Block 1	410.0	(16.9)	421.2	(20.9)	425.4	(16.7)	443.9	(22.2)
Block2	448.8	(17.5)	449.7	(18.0)	475.7	(12.7)	471.7	(21.1)
Combined	429.1	(16.8)	435.8	(18.6)	450.7	(14.1)	457.9	(21.1)
Hit Rate (%)	M	(SE)	M	(SE)	M	(SE)	M	(SE)
Block 1	93.1	(2.0)	90.2	(2.3)	89.9	(2.0)	88.2	(2.8)
Block2	85.1	(3.4)	88.8	(2.2)	83.1	(2.7)	85.3	(3.0)
Combined	89.1	(2.6)	89.7	(2.0)	86.4	(1.9)	86.9	(2.7)
False Alarms (%)	M	(SE)	M	(SE)	M	(SE)	M	(SE)
Block 1	3.5	(1.1)	2.5	(0.6)	4.1	(1.2)	3.9	(1.3)
Block2	4.1	(1.4)	2.9	(7.3)	5.3	(1.8)	3.5	(1.1)
Combined	3.7	(1.2)	2.6	(0.6)	4.6	(1.5)	3.4	(1.2)
<i>A prime</i>	M	(SE)	M	(SE)	M	(SE)	M	(SE)
Block 1	0.97	(0.00)	0.97	(0.00)	0.96	(0.00)	0.96	(0.01)
Block2	0.95	(0.01)	0.96	(0.00)	0.94	(0.01)	0.95	(0.01)
Combined	0.96	(0.01)	0.97	(0.00)	0.95	(0.00)	0.95	(0.01)

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<i>Beta</i>	M	(SE)	M	(SE)	M	(SE)	M	(SE)
Block 1	0.28	(0.10)	0.51	(0.12)	0.43	(0.09)	0.47	(0.09)
Block2	0.48	(0.07)	0.56	(0.08)	0.55	(0.07)	0.58	(0.09)
Combined	0.42	(0.07)	0.57	(0.09)	0.52	(0.07)	0.52	(0.09)

Table 22

CPT ERPs: Pre- versus Follow-up (1 week) Post-treatment Effects, Averaged Across the Two Time Blocks, on Rare and Frequent P300 Amplitudes (μV) at 3 (FZ,CZ,PZ) Scalp Sites (N=14)

	Placebo				Nicotine			
	Pre		Post		Pre		Post	
Rare								
scalp site	M	(SE)	M	(SE)	M	(SE)	M	(SE)
FZ	3.3	(1.0)	3.3	(1.0)	4.0	(1.3)	3.8	(1.0)
CZ	10.9	(1.5)	9.5	(1.7)	9.5	(1.3)	9.2	(1.4)
PZ	14.4	(1.3)	13.2	(1.3)	13.1	(1.2)	12.5	(1.2)
Frequent								
scalp site	M	(SE)	M	(SE)	M	(SE)	M	(SE)
FZ	2.3	(0.6)	3.1	(1.0)	3.1	(0.7)	2.7	(0.7)
CZ	5.3	(0.6)	4.9	(0.8)	5.5	(0.6)	4.9	(0.7)
PZ	5.8	(0.5)	4.3	(0.5)	5.5	(0.8)	4.7	(0.6)

Table 23

CPT ERPs: Pre- versus Follow-up (1 week) Post-treatment Effects, Averaged Across the Two Time Blocks, on Rare and Frequent P300 Latencies (ms) at 3 (FZ,CZ,PZ) Scalp Sites (N=14)

Placebo					Nicotine			
Pre		Post		Pre		Post		
Rare								
scalp site	M	(SE)	M	(SE)	M	(SE)	M	(SE)
FZ	410.3	(26.6)	461.2	(25.0)	441.8	(21.2)	405.0	(19.3)
CZ	437.4	(19.7)	453.0	(17.6)	437.8	(16.4)	444.2	(16.6)
PZ	452.3	(14.4)	457.3	(11.0)	449.6	(10.2)	456.0	(17.7)
Frequent								
scalp site	M	(SE)	M	(SE)	M	(SE)	M	(SE)
FZ	411.4	(21.7)	449.1	(24.6)	440.3	(22.7)	412.8	(18.2)
CZ	413.3	(20.4)	434.8	(22.9)	473.7	(24.0)	436.8	(24.6)
PZ	497.4	(25.1)	485.2	(24.9)	492.7	(21.4)	476.4	(26.4)

Table 24

CPT ERPs: Mean (+/-SE) Pre- versus Follow-up (1 week) Post-treatment Effects on Rare and Frequent P300 Amplitudes (μV) at PZ Scalp Site, with Respect to Separate and Combined Time Blocks (N=14)

	Placebo				Nicotine			
	Pre		Post		Pre		Post	
Rare								
PZ	M	(SE)	M	(SE)	M	(SE)	M	(SE)
Block 1	16.3	(1.8)	14.5	(1.5)	13.7	(1.3)	13.8	(1.2)
Block 2	14.1	(0.9)	12.6	(1.4)	13.1	(1.6)	12.6	(1.8)
Combined	14.4	(1.3)	13.2	(1.3)	13.1	(1.2)	12.5	(1.2)
Frequent								
PZ	M	(SE)	M	(SE)	M	(SE)	M	(SE)
Block 1	6.2	(0.7)	5.2	(0.5)	5.5	(0.9)	5.7	(0.6)
Block 2	5.8	(0.5)	4.5	(0.7)	6.3	(0.9)	4.4	(0.8)
Combined	5.8	(0.5)	4.3	(0.5)	5.6	(0.8)	4.7	(0.6)

Table 25

CPT ERPs: Mean (+/-SE) Pre- versus Follow-up (1 week) Post-treatment Effects on Rare and Frequent P300 Latencies (ms) at PZ Scalp Site, with Respect to Separate and Combined Time Blocks (N=14)

	Placebo				Nicotine			
	Pre		Post		Pre		Post	
Rare								
PZ	M	(SE)	M	(SE)	M	(SE)	M	(SE)
Block 1	452.5	(13.5)	448.3	(10.9)	442.5	(9.6)	435.2	(13.9)
Block 2	455.4	(19.5)	459.8	(15.6)	456.8	(11.8)	423.7	(17.5)
Combined	452.3	(14.5)	457.3	(11.0)	449.6	(10.2)	455.9	(17.7)
Frequent								
PZ	M	(SE)	M	(SE)	M	(SE)	M	(SE)
Block 1	455.6	(26.9)	486.1	(24.8)	490.7	(21.9)	469.8	(26.3)
Block 2	509.1	(23.9)	467.4	(23.2)	512.5	(27.5)	480.1	(25.9)
Combined	497.4	(25.1)	485.2	(24.9)	492.7	(21.4)	476.4	(26.4)

Table 26

CPT ERPs: Pre- versus Follow-up (1 week) Post-treatment Effects on Four P300 Area (summed μV) Means (+/- SE) at 3 (FZ, CZ, PZ) Scalp Sites for Rare Stimuli, Averaged Across the Two Time Blocks (N=14)

	Placebo				Nicotine			
	Pre		Post		Pre		Post	
FZ (summed μV)								
	M	(SE)	M	(SE)	M	(SE)	M	(SE)
Area 1	-39.3	(29.7)	-66.4	(32.7)	-23.6	(48.6)	8.2	(39.8)
Area 2	-18.2	(45.8)	18.1	(53.5)	10.4	(61.3)	40.8	(41.2)
Area 3	-67.6	(46.7)	31.1	(50.1)	20.8	(47.1)	5.6	(37.8)
Area 4	-85.9	(48.4)	3.0	(35.0)	-16.6	(45.2)	-50.2	(38.5)
CZ (summed μV)								
	M	(SE)	M	(SE)	M	(SE)	M	(SE)
Area 1	201.9	(54.3)	106.5	(52.9)	142.2	(52.8)	184.1	(53.3)
Area 2	313.3	(72.7)	273.5	(69.4)	240.0	(65.1)	275.9	(56.9)
Area 3	259.6	(60.4)	259.7	(65.1)	245.0	(52.1)	251.6	(60.5)
Area 4	217.5	(65.2)	166.2	(59.6)	192.2	(44.7)	171.8	(64.8)
PZ (summed μV)								
	M	(SE)	M	(SE)	M	(SE)	M	(SE)
Area 1	326.6	(56.3)	226.1	(52.0)	227.4	(50.1)	261.0	(47.2)
Area 2	499.3	(57.0)	412.3	(60.4)	395.5	(58.9)	397.4	(47.0)
Area 3	457.6	(44.0)	416.6	(51.2)	407.8	(42.0)	365.3	(48.9)
Area 4	367.0	(42.7)	270.8	(51.7)	306.1	(36.3)	254.5	(55.9)

Note: Area 1 = 300-375 ms
Area 2 = 375-450 ms

Area 3 = 450-525 ms
Area 4 = 525-600 ms

Table 27

CPT ERPs: Pre- versus Follow-up (1 week) Post-treatment Effects on Four P300 Area (summed μV) Means (+/- SE) at 3 (FZ, CZ, PZ) Scalp Sites for Frequent Stimuli, Averaged Across the Two Time Blocks (N=14)

	Placebo				Nicotine			
	Pre		Post		Pre		Post	
	M	(SE)	M	(SE)	M	(SE)	M	(SE)
FZ (summed μV)								
Area 1	-37.3	(15.1)	-44.1	(12.7)	-24.6	(18.8)	-3.0	(22.1)
Area 2	13.3	(32.8)	18.6	(35.5)	21.4	(23.9)	9.9	(32.4)
Area 3	-42.6	(32.2)	1.6	(57.2)	0.5	(35.3)	-24.3	(38.2)
Area 4	-64.2	(29.9)	0.7	(42.0)	-26.4	(24.3)	-21.3	(26.8)
CZ (summed μV)								
	M	(SE)	M	(SE)	M	(SE)	M	(SE)
Area 1	67.7	(18.8)	40.3	(24.9)	51.3	(22.9)	60.4	(26.4)
Area 2	131.1	(33.9)	104.4	(29.9)	118.6	(30.2)	87.8	(36.3)
Area 3	85.5	(39.6)	92.3	(39.6)	107.6	(31.4)	62.6	(46.3)
Area 4	74.1	(35.4)	98.9	(31.6)	92.9	(22.4)	69.0	(36.9)
PZ (summed μV)								
	M	(SE)	M	(SE)	M	(SE)	M	(SE)
Area 1	81.3	(21.9)	19.8	(24.5)	46.6	(27.0)	35.7	(25.2)
Area 2	153.1	(23.1)	91.1	(24.2)	131.9	(28.8)	79.7	(36.9)
Area 3	111.9	(32.2)	63.9	(26.1)	109.3	(32.5)	49.3	(46.8)
Area 4	97.5	(34.9)	86.0	(24.7)	96.1	(32.6)	65.5	(37.6)

Note: Area 1 = 300-375 ms
Area 2 = 375-450 ms

Area 3 = 450-525 ms
Area 4 = 525-600 ms

Table 28

Intercorrelations between Conners' Parent Rating Scale (CPRS) Indices and Child Behavior**Checklist (CBCL) Attention Problems Index (N=11)**

Indices	1	2	3	4	5	6	7
1. CPRS (B): Cognitive Problems/ Inattentive	--	.45	.74**	.58	.88**	.65*	.49
2. CPRS (C): Hyperactivity		--	.66*	.89**	.50	.88**	.39
3. CPRS (K): ADHD Index			--	.84**	.87**	.90**	.22
4. CPRS (I): Global Index: Total				--	.63*	.91**	.30
5. CPRS (L): DSM-IV: Inattentive					--	.76**	.43
6. CPRS (N): DSM-IV: Total						--	.25
7. BCL: Attention Problems							--

* Correlation is significant at the 0.05 level (2-tailed)

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

Table 29

**Correlation Coefficients between Conners' Parent Rating Scale (CPRS) Cognitive Problems/
Inattentive Index, Child Behavior Checklist (CBCL) Attention Problems Index, and Other
Attentional Measures (N=11)**

Indices	1	2	3	4	5	6	7	8	9
1. CPRS: Cognitive Problems /Inattentive	--	.49	.53	.31	.23	.01	.10	-.07	.20
2. CBCL: Attention Problems		--	.61*	.08	-.18	-.24	-.06	-.15	.34
3. Digit Span: scaled score			--	.53	.34	-.14	-.29	.04	.75**
4. Coding : scaled score				--	.23	.30	-.42	.39	.44
5. CPT: Reaction time					--	-.03	.03	-.04	.42
6. CPT: Hit rate						--	-.57	.90**	-.11
7. CPT: False Alarms							--	-.87**	-.53
8. CPT: A Prime								--	.21
9. CPT: Beta									--

* Correlation is significant at the 0.05 level (2-tailed)

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

Figure 1

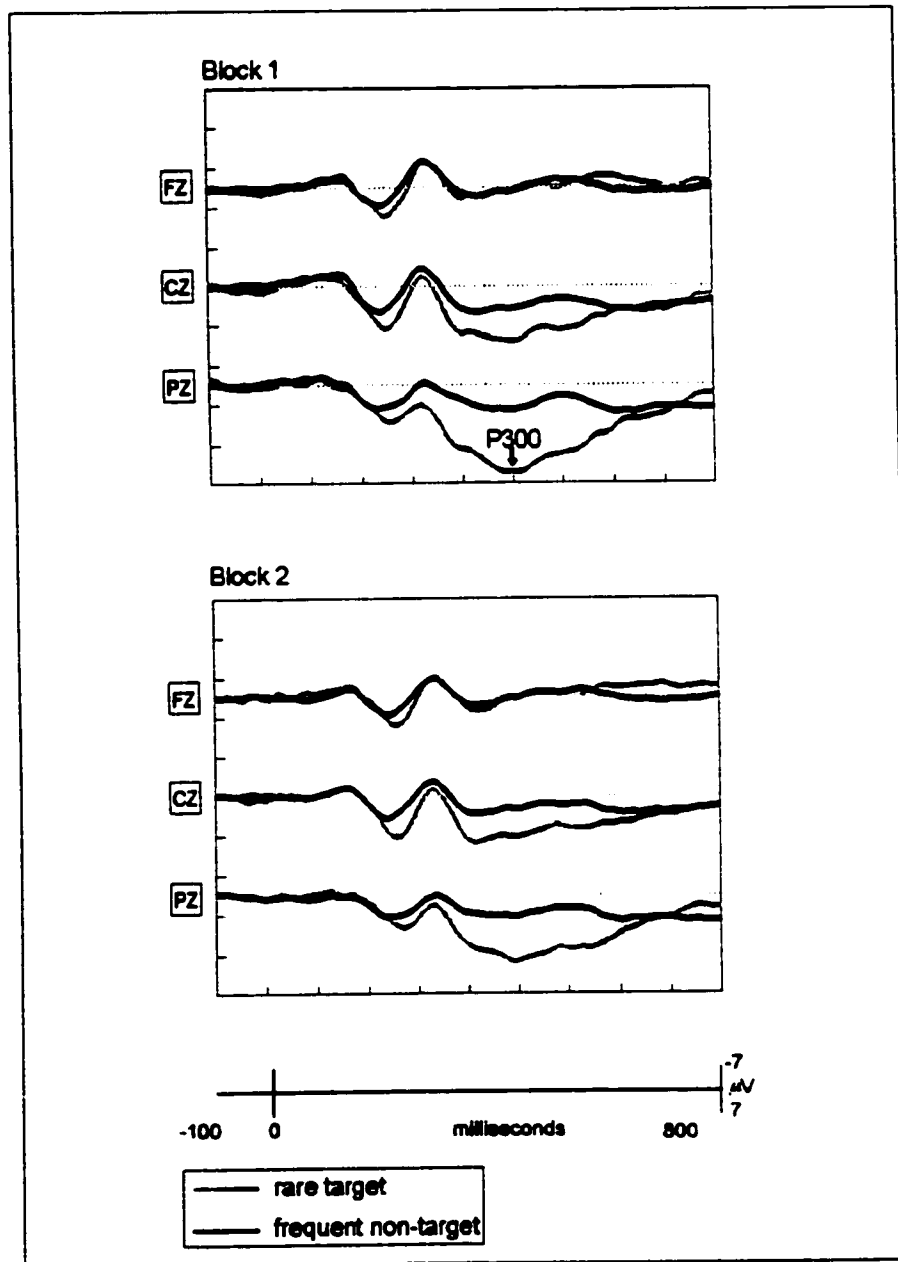


Figure 1. Grand-averaged P300 waveforms for the first session for all subjects (N=14), showing overlapping rare and frequent waves at each scalp site (FZ, CZ, PZ) for each block.

Figure 2

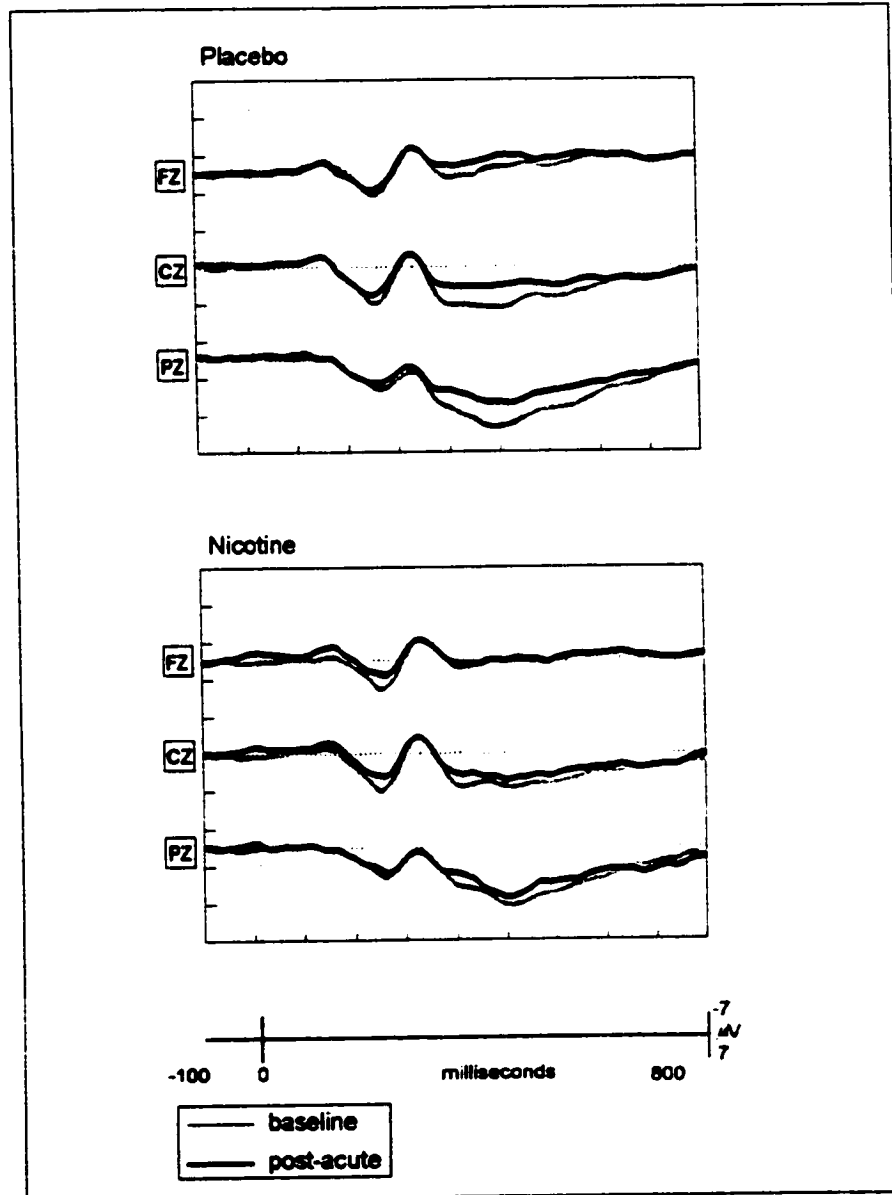


Figure 2. Pre-treatment baseline versus acute (4 hours) post-treatment P300 waveforms following rare (target) stimuli, averaged across the two time blocks, at three (FZ, CZ, PZ) scalp sites.

Figure 3

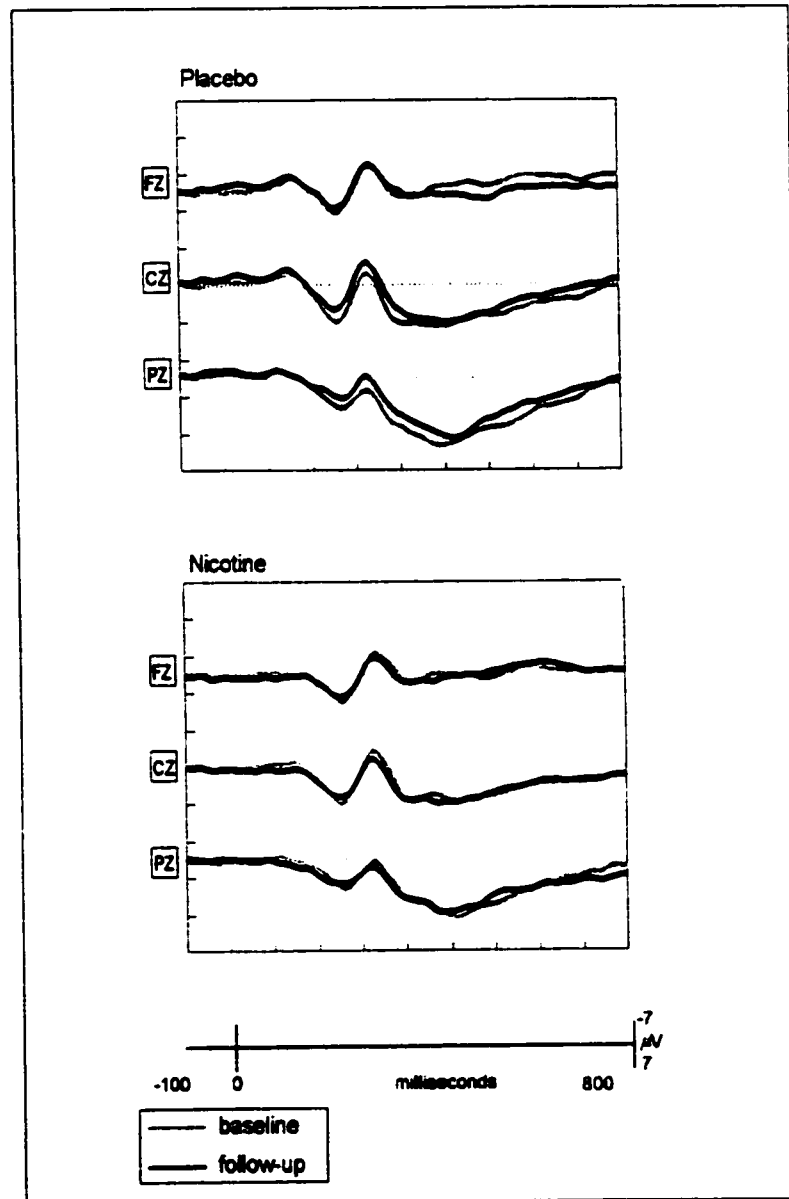


Figure 3. Pre-treatment baseline versus follow-up (1 week) post-treatment P300 waveforms following rare (target) stimuli, averaged across the two time blocks, at three (FZ, CZ, PZ) scalp sites.

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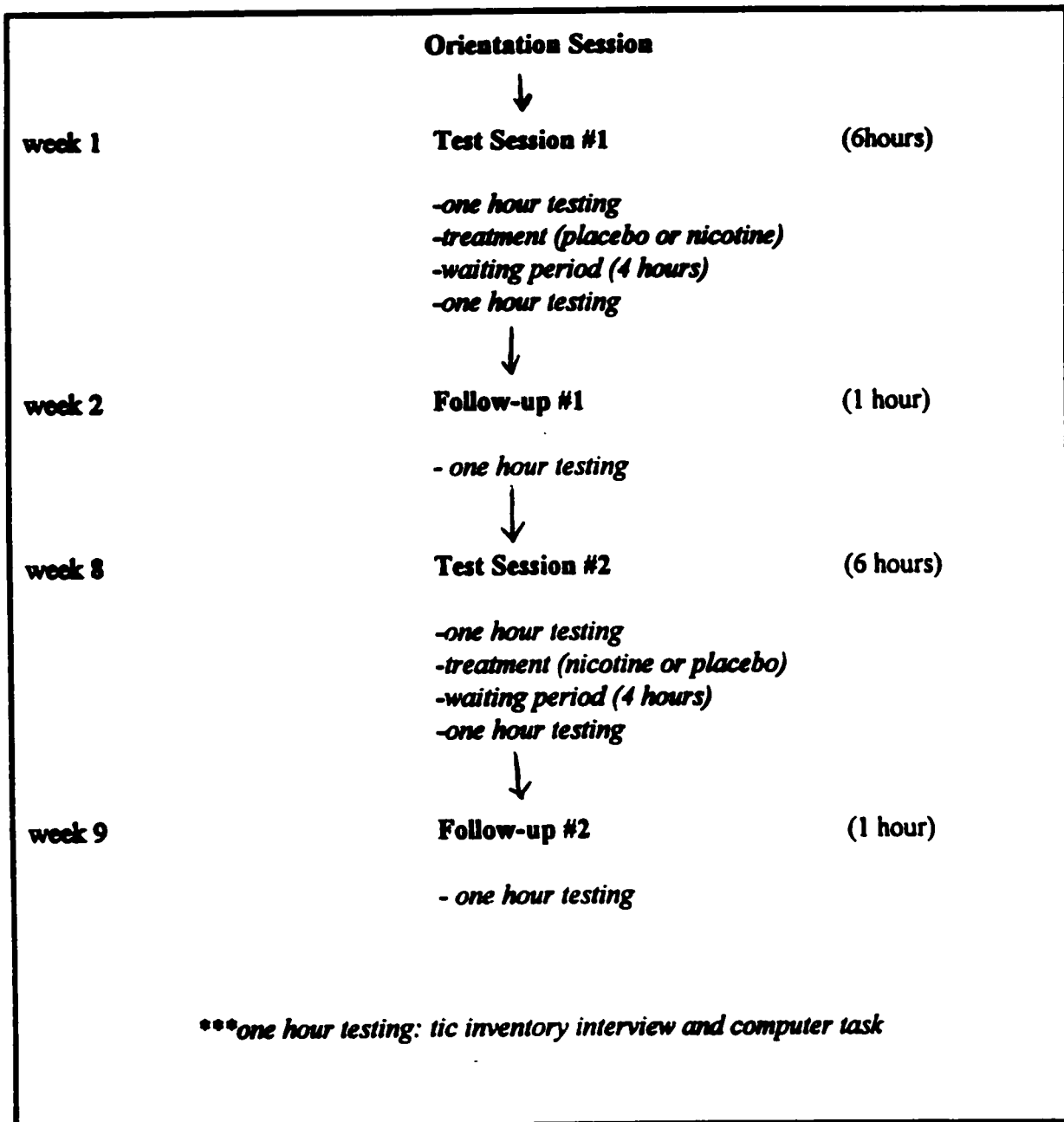
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Clinical Global Impression Scales for TS, OCD

A. TS-Clinical Global Impression Scale

This scale is based on all available information concerning the adverse impact of clearly defined *tic* behaviors on the individual's life.

<i>Normal</i>	No tic symptoms.
<i>Borderline</i>	Questionable tic symptoms. Does not satisfy criteria for a diagnosis of a definite chronic tic disorder.
<i>Mild</i>	Satisfies DSM-III criteria for a chronic tic disorder. Symptoms do not interfere and are not noticeable to most people.
<i>Moderate</i>	Tic symptoms cause some problems in some areas of functioning and are noticeable to some* people some of the time.
<i>Marked</i>	Tic symptoms cause clear problems in more than one area of functioning. Tics are usually frequent and quite noticeable in most situations most of the time.
<i>Severe</i>	Tic symptoms cause significant impairment in primary social role such that functioning in "usual" settings is impossible or in serious jeopardy.
<i>Extremely Severe</i>	Tic symptoms are incapacitating and/or have caused serious physical injury.



TOURETTE'S STUDY

Testing Date:

Test Session #

NAME:

CODE: TS01

D.O.B.:

COMMENTS:

- _____ (8:30) Arrival at lab - subject file no.
- _____ (8:40) Parent - CBCL, Conner's & TSSL for past week
- _____ (8:45) Child to CB1031 wait in hall
 - Record ! (and check date)
 - 5 minute TSSL day before
 - 5 minute Relax
 - 5 minute Digit Span / Digit Symbol
 - Standby ! (& choose movie !)
- _____ (9:00) EEG Hookup #1 and **practice** sessions given
 - monitor 1 meter check
 - naision to inion
 - BP ___ / ___
 - heart rate ___
- _____ (9:30) CPT 11 minutes
 - STIM (file name) _____
 - SCAN (file name) _____
 - F2 for Muscle Artefact

Recording comments:

- _____ (9:45) Remove electrodes & Adverse event list (pre-treatment)
- _____ (9:50) Apply treatment patch (Colleen)
- (9:55) Snack, walk to Subway
- (10:30) Movie

Adverse Reaction Checklist and Comments:

_____ (9:50 to 1:50 pm) **4 hour Waiting Period**

_____ (10:50) A/E

_____ (11:50) A/E

_____ (12:30) Lunch

_____ (12:50) A/E

_____ (1:00) Child to CB1031 (wait in hall)

- Record ! (and check date)
- 5 minute TSSL day before
- 5 minute Relax
- 5 minute Digit Span / Digit Symbol
- Standby !

_____ (1:20) EEG Hookup #2

- BP ____/____
- heart rate ____

_____ (1:50) A/E

_____ (2:00) CPT 11 minutes

- STIM (file name) _____
- SCAN (file name) _____
- F2 for Muscle Artefact

Recording comments:

_____ Remove electrodes & Hot face cloth
 (2:15) Remove treatment patch (Colleen)
 Clean up

_____ (2:20) Give out TSSL, next appointment card (1 week or 7 weeks), & Parking Ticket

Comments:

Clinical and Attentional Effects of Acute Nicotine Treatment in Tourette's Disorder

Subject:

Date:

Test #

Parent	Child	Orienta- tion	Test #1	Follow- up #1	Test #2	Follow- up #2
Consent	Assent					
CBCL						
Conner's						
TSSL						
	Clinical (video)					
	BP & HR					
	CPT					
	Adverse Event #1 (0)					
	Patch (Initials)					
	Snack / Walk					
	Adverse Event #2 (+1)					
	Adverse Event #3 (+2)					
	Adverse Event #4 (+3)					
	Clinical (video)					
	BP & HR					
	Adverse Event #5 (+4)					
	CPT					
	Remove Patch (Initials)					
	Appointment card					
	Parking Ticket					

CHILD BEHAVIOR CHECKLIST FOR AGES 4-18

APPENDIX D

Please Print

CHILD'S FULL NAME		FIRST	MIDDLE	LAST	PARENTS' USUAL TYPE OF WORK, even if not working now. (Please be specific—for example, auto mechanic, high school teacher, homemaker, laborer, lathe operator, shoe salesman, army sergeant.) FATHER'S TYPE OF WORK: _____ MOTHER'S TYPE OF WORK: _____ THIS FORM FILLED OUT BY: ☐ Mother (full name) _____ ☐ Father (full name) _____ ☐ Other—full name & relationship to child: _____
SEX ☐ Boy ☐ Girl	AGE	ETHNIC GROUP OR RACE			
TODAY'S DATE Mo. _____ Date _____ Yr. _____		CHILD'S BIRTHDATE Mo. _____ Date _____ Yr. _____			
GRADE IN SCHOOL _____		Please fill out this form to reflect your view of the child's behavior even if other people might not agree. Feel free to print additional comments beside each item and in the spaces provided on page 2.			
NOT ATTENDING SCHOOL ☐					

I. Please list the sports your child most likes to take part in. For example: swimming, baseball, skating, skate boarding, bike riding, fishing, etc. ☐ None	Compared to others of the same age, about how much time does he/she spend in each?	Compared to others of the same age, how well does he/she do each one?
	Don't Know Less Than Average Average More Than Average	Don't Know Below Average Average Above Average
a. _____	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐
b. _____	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐
c. _____	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐
II. Please list your child's favorite hobbies, activities, and games, other than sports. For example: stamps, dolls, books, piano, crafts, cars, singing, etc. (Do not include listening to radio or TV.) ☐ None	Compared to others of the same age, about how much time does he/she spend in each?	Compared to others of the same age, how well does he/she do each one?
	Don't Know Less Than Average Average More Than Average	Don't Know Below Average Average Above Average
a. _____	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐
b. _____	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐
c. _____	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐
III. Please list any organizations, clubs, teams, or groups your child belongs to. ☐ None	Compared to others of the same age, how active is he/she in each?	
	Don't Know Less Active Average More Active	
a. _____	☐ ☐ ☐ ☐	
b. _____	☐ ☐ ☐ ☐	
c. _____	☐ ☐ ☐ ☐	
IV. Please list any jobs or chores your child has. For example: paper route, babysitting, making bed, working in store, etc. (Include both paid and unpaid jobs and chores.) ☐ None	Compared to others of the same age, how well does he/she carry them out?	
	Don't Know Below Average Average Above Average	
a. _____	☐ ☐ ☐ ☐	
b. _____	☐ ☐ ☐ ☐	
c. _____	☐ ☐ ☐ ☐	

- V. 1. About how many close friends does your child have? ☐ None ☐ 1 ☐ 2 ☐ 3 or more
(Do not include brothers & sisters)
2. About how many times a week does your child do things with any friends outside of regular school hours?
(Do not include brothers & sisters) ☐ Less than 1 ☐ 1 or 2 ☐ 3 or more

VI. Compared to others of his/her age, how well does your child:

	Worse	About Average	Better	
a. Get along with his/her brothers & sisters?	☐	☐	☐	☐ Has no brothers or sisters
b. Get along with other kids?	☐	☐	☐	
c. Behave with his/her parents?	☐	☐	☐	
d. Play and work alone?	☐	☐	☐	

VII. 1. For ages 6 and older—performance in academic subjects. ☐ Does not attend school because _____

Check a box for each subject that child takes

	Failing	Below Average	Average	Above Average
a. Reading, English, or Language Arts	☐	☐	☐	☐
b. History or Social Studies	☐	☐	☐	☐
c. Arithmetic or Math	☐	☐	☐	☐
d. Science	☐	☐	☐	☐

Other academic subjects — for example: computer courses, foreign language, business. Do not include gym, shop, driver's ed., etc.

e. _____	☐	☐	☐	☐
f. _____	☐	☐	☐	☐
g. _____	☐	☐	☐	☐

2. Does your child receive special remedial services or attend a special class or special school? ☐ No ☐ Yes—kind of services, class, or school: _____

3. Has your child repeated any grades? ☐ No ☐ Yes—grades and reasons: _____

4. Has your child had any academic or other problems in school? ☐ No ☐ Yes—please describe: _____

When did these problems start? _____

Have these problems ended? ☐ No ☐ Yes—when? _____

Does your child have any illness or disability (either physical or mental)? ☐ No ☐ Yes—please describe: _____

What concerns you most about your child? _____

Please describe the best things about your child: _____

0 = Not True (as far as you know) 1 = Somewhat or Sometimes True 2 = Very True or Often True

- 0 1 2 1. Acts too young for his/her age
- 0 1 2 2. Allergy (describe): _____
- 0 1 2 3. Argues a lot
- 0 1 2 4. Asthma
- 0 1 2 5. Behaves like opposite sex
- 0 1 2 6. Bowel movements outside toilet
- 0 1 2 7. Bragging, boasting
- 0 1 2 8. Can't concentrate, can't pay attention for long
- 0 1 2 9. Can't get his/her mind off certain thoughts; obsessions (describe): _____
- 0 1 2 10. Can't sit still, restless, or hyperactive
- 0 1 2 11. Clings to adults or too dependent
- 0 1 2 12. Complains of loneliness
- 0 1 2 13. Confused or seems to be in a fog
- 0 1 2 14. Cries a lot
- 0 1 2 15. Cruel to animals
- 0 1 2 16. Cruelty, bullying, or meanness to others
- 0 1 2 17. Day-dreams or gets lost in his/her thoughts
- 0 1 2 18. Deliberately harms self or attempts suicide
- 0 1 2 19. Demands a lot of attention
- 0 1 2 20. Destroys his/her own things
- 0 1 2 21. Destroys things belonging to his/her family or others
- 0 1 2 22. Disobedient at home
- 0 1 2 23. Disobedient at school
- 0 1 2 24. Doesn't eat well
- 0 1 2 25. Doesn't get along with other kids
- 0 1 2 26. Doesn't seem to feel guilty after misbehaving
- 0 1 2 27. Easily jealous
- 0 1 2 28. Eats or drinks things that are not food – don't include sweets (describe): _____
- 0 1 2 29. Fears certain animals, situations, or places, other than school (describe): _____
- 0 1 2 30. Fears going to school

- 0 1 2 31. Fears he/she might think or do something bad
- 0 1 2 32. Feels he/she has to be perfect
- 0 1 2 33. Feels or complains that no one loves him/her
- 0 1 2 34. Feels others are out to get him/her
- 0 1 2 35. Feels worthless or inferior
- 0 1 2 36. Gets hurt a lot, accident-prone
- 0 1 2 37. Gets in many fights
- 0 1 2 38. Gets teased a lot
- 0 1 2 39. Hangs around with others who get in trouble
- 0 1 2 40. Hears sounds or voices that aren't there (describe): _____
- 0 1 2 41. Impulsive or acts without thinking
- 0 1 2 42. Would rather be alone than with others
- 0 1 2 43. Lying or cheating
- 0 1 2 44. Bites fingernails
- 0 1 2 45. Nervous, highstrung, or tense
- 0 1 2 46. Nervous movements or twitching (describe): _____
- 0 1 2 47. Nightmares
- 0 1 2 48. Not liked by other kids
- 0 1 2 49. Constipated, doesn't move bowels
- 0 1 2 50. Too fearful or anxious
- 0 1 2 51. Feels dizzy
- 0 1 2 52. Feels too guilty
- 0 1 2 53. Overeating
- 0 1 2 54. Overtired
- 0 1 2 55. Overweight
56. Physical problems *without known medical cause*:
- 0 1 2 a. Aches or pains (not stomach or headaches)
- 0 1 2 b. Headaches
- 0 1 2 c. Nausea, feels sick
- 0 1 2 d. Problems with eyes (not if corrected by glasses) (describe): _____
- 0 1 2 e. Rashes or other skin problems
- 0 1 2 f. Stomachaches or cramps
- 0 1 2 g. Vomiting, throwing up
- 0 1 2 h. Other (describe): _____

Please see other side

- 0 1 2 58. Picks nose, skin, or other parts of body (describe): _____
- 0 1 2 59. Plays with own sex parts in public
- 0 1 2 60. Plays with own sex parts too much
- 0 1 2 61. Poor school work
- 0 1 2 62. Poorly coordinated or clumsy
- 0 1 2 63. Prefers being with older kids
- 0 1 2 64. Prefers being with younger kids
- 0 1 2 65. Refuses to talk
- 0 1 2 66. Repeats certain acts over and over; compulsions (describe): _____
- 0 1 2 67. Runs away from home
- 0 1 2 68. Screams a lot
- 0 1 2 69. Secretive, keeps things to self
- 0 1 2 70. Sees things that aren't there (describe): _____
- 0 1 2 71. Self-conscious or easily embarrassed
- 0 1 2 72. Sets fires
- 0 1 2 73. Sexual problems (describe): _____
- 0 1 2 74. Showing off or clowning
- 0 1 2 75. Shy or timid
- 0 1 2 76. Sleeps less than most kids
- 0 1 2 77. Sleeps more than most kids during day and/or night (describe): _____
- 0 1 2 78. Smears or plays with bowel movements
- 0 1 2 79. Speech problem (describe): _____
- 0 1 2 80. Stares blankly
- 0 1 2 81. Steals at home
- 0 1 2 82. Steals outside the home
- 0 1 2 83. Stores up things he/she doesn't need (describe): _____

- 0 1 2 85. Strange ideas (describe): _____
- 0 1 2 86. Stubborn, sullen, or irritable
- 0 1 2 87. Sudden changes in mood or feelings
- 0 1 2 88. Sulks a lot
- 0 1 2 89. Suspicious
- 0 1 2 90. Swearing or obscene language
- 0 1 2 91. Talks about killing self
- 0 1 2 92. Talks or walks in sleep (describe): _____
- 0 1 2 93. Talks too much
- 0 1 2 94. Teases a lot
- 0 1 2 95. Temper tantrums or hot temper
- 0 1 2 96. Thinks about sex too much
- 0 1 2 97. Threatens people
- 0 1 2 98. Thumb-sucking
- 0 1 2 99. Too concerned with neatness or cleanliness
- 0 1 2 100. Trouble sleeping (describe): _____
- 0 1 2 101. Truancy, skips school
- 0 1 2 102. Underactive, slow moving, or lacks energy
- 0 1 2 103. Unhappy, sad, or depressed
- 0 1 2 104. Unusually loud
- 0 1 2 105. Uses alcohol or drugs for nonmedical purposes (describe): _____
- 0 1 2 106. Vandalism
- 0 1 2 107. Wets self during the day
- 0 1 2 108. Wets the bed
- 0 1 2 109. Whining
- 0 1 2 110. Wishes to be of opposite sex
- 0 1 2 111. Withdrawn, doesn't get involved with others
- 0 1 2 112. Worries
113. Please write in any problems your child has that were not listed above: _____
- 0 1 2 _____
- 0 1 2 _____
- 0 1 2 _____

PLEASE BE SURE YOU HAVE ANSWERED ALL ITEMS.

PAGE 4

UNDERLINE ANY YOU ARE CONCERNED ABOUT

QUESTIONNAIRE DE COMPORTEMENT D'ACHENBACH

VERSION PARENTS (Traduction par Francine Lussier Ph.D. - Hôpital Ste-Justine)

NOM DE L'ENFANT: _____

SEXE: Garçon fille
☐ ☐

AGE: _____

DATE DU TEST: jour _____ mois _____ an _____
 NAISSANCE: jour _____ mois _____ an _____

DEGRE SCOLAIRE: _____

FREQUENTE ACTUELLEMENT L'ECOLE: oui non
☐ ☐

Travail habituel des parents même si sans emploi présentement:

TYPE DU TRAVAIL DU PERE: _____

TYPE DU TRAVAIL DE LA MERE: _____

CE QUESTIONNAIRE A ETE REMPLI PAR:

le père (nom): _____

la mère (nom): _____

autre (nom et relation avec l'enfant): _____

Prière de remplir le questionnaire au meilleur de votre connaissance sans laisser d'espace vide. Ajouter des commentaires au besoin.

I- Faites la liste des sports auxquels votre enfant aime le plus participer. Par exemple, natation, baseball, patinage, rouleur (skate board), bicyclette, pêche etc. ☐ aucun a) _____ b) _____ c) _____	Comparé aux autres enfants de son âge, environ combien de temps passe-t-il pour chacun de ces sports? <table border="1"> <thead> <tr> <th>je ne sais pas</th> <th>moins que la moyenne</th> <th>dans la moyenne</th> <th>plus que la moyenne</th> </tr> </thead> <tbody> <tr> <td>☐</td> <td>☐</td> <td>☐</td> <td>☐</td> </tr> <tr> <td>☐</td> <td>☐</td> <td>☐</td> <td>☐</td> </tr> <tr> <td>☐</td> <td>☐</td> <td>☐</td> <td>☐</td> </tr> </tbody> </table>	je ne sais pas	moins que la moyenne	dans la moyenne	plus que la moyenne	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Comparé aux autres enfants du même âge comment réussit-il/elle dans chacun de ces sports? <table border="1"> <thead> <tr> <th>je ne sais pas</th> <th>sous la moyenne</th> <th>dans la moyenne</th> <th>au dessus de la moyenne</th> </tr> </thead> <tbody> <tr> <td>☐</td> <td>☐</td> <td>☐</td> <td>☐</td> </tr> <tr> <td>☐</td> <td>☐</td> <td>☐</td> <td>☐</td> </tr> <tr> <td>☐</td> <td>☐</td> <td>☐</td> <td>☐</td> </tr> </tbody> </table>	je ne sais pas	sous la moyenne	dans la moyenne	au dessus de la moyenne	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
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☐	☐	☐	☐																															
II- Énumérez tous les passe-temps (hobby), activités, jeux favoris de votre enfant autres que les sports. Par exemple, timbres, poupées, lecture, piano, artisanat, chant, etc.... sans inclure la télévision. ☐ aucun a) _____ b) _____ c) _____	Comparé aux autres enfants de son âge, environ combien de temps passe-t-il pour chacune de ces activités? <table border="1"> <thead> <tr> <th>je ne sais pas</th> <th>moins que la moyenne</th> <th>dans la moyenne</th> <th>plus que la moyenne</th> </tr> </thead> <tbody> <tr> <td>☐</td> <td>☐</td> <td>☐</td> <td>☐</td> </tr> <tr> <td>☐</td> <td>☐</td> <td>☐</td> <td>☐</td> </tr> <tr> <td>☐</td> <td>☐</td> <td>☐</td> <td>☐</td> </tr> </tbody> </table>	je ne sais pas	moins que la moyenne	dans la moyenne	plus que la moyenne	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Comparé aux autres enfants du même âge comment réussit-il/elle dans chacune de ces activités? <table border="1"> <thead> <tr> <th>je ne sais pas</th> <th>sous la moyenne</th> <th>dans la moyenne</th> <th>au dessus de la moyenne</th> </tr> </thead> <tbody> <tr> <td>☐</td> <td>☐</td> <td>☐</td> <td>☐</td> </tr> <tr> <td>☐</td> <td>☐</td> <td>☐</td> <td>☐</td> </tr> <tr> <td>☐</td> <td>☐</td> <td>☐</td> <td>☐</td> </tr> </tbody> </table>	je ne sais pas	sous la moyenne	dans la moyenne	au dessus de la moyenne	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
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III- Donnez le nom de toutes les organisations, clubs, équipes ou groupes auxquels votre enfant appartient. ☐ aucun a) _____ b) _____ c) _____	Comparé aux autres enfants du même âge, comment est-il actif dans chacun? <table border="1"> <thead> <tr> <th>je ne sais pas</th> <th>moins actif</th> <th>dans la moyenne</th> <th>plus actif</th> </tr> </thead> <tbody> <tr> <td>☐</td> <td>☐</td> <td>☐</td> <td>☐</td> </tr> <tr> <td>☐</td> <td>☐</td> <td>☐</td> <td>☐</td> </tr> <tr> <td>☐</td> <td>☐</td> <td>☐</td> <td>☐</td> </tr> </tbody> </table>	je ne sais pas	moins actif	dans la moyenne	plus actif	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐																	
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☐	☐	☐	☐																															
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☐	☐	☐	☐																															
IV- Énumérez tous les emplois ou tâches de votre enfant. Par exemple, distribution de journaux, gardiennage, faire le lit, etc. (inclure les travaux et tâches payés ou non). ☐ aucun a) _____ b) _____ c) _____	Comparé aux autres enfants de son âge comment les exécute-t-il? <table border="1"> <thead> <tr> <th>je ne sais pas</th> <th>sous la moyenne</th> <th>dans la moyenne</th> <th>au dessus de la moyenne</th> </tr> </thead> <tbody> <tr> <td>☐</td> <td>☐</td> <td>☐</td> <td>☐</td> </tr> <tr> <td>☐</td> <td>☐</td> <td>☐</td> <td>☐</td> </tr> <tr> <td>☐</td> <td>☐</td> <td>☐</td> <td>☐</td> </tr> </tbody> </table>	je ne sais pas	sous la moyenne	dans la moyenne	au dessus de la moyenne	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐																	
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aucun ☐ 1 ☐ 2 ou 3 ☐ 4 ☐

2. A peu près combien de fois par semaine votre enfant a-t-il des activités avec ses amis en dehors des heures scolaires?

moins qu'une fois ☐ 1 ou 2 fois ☐ 3 fois ou plus ☐

VI- Comparé aux autres enfants de son âge, comment votre enfant

	pire	moyen	mieux
a) s'entend-il avec ses frères et soeurs	☐	☐	☐
b) s'entend-il avec les autres enfants?	☐	☐	☐
c) se comporte-t-il avec ses parents?	☐	☐	☐
d) joue-t-il ou travaille-t-il par lui-même?	☐	☐	☐

VII-1. Pour les enfants de 6 ans et plus: résultats scolaires (si l'enfant ne va pas à l'école S.V.P. donnez-en la raison)

	Echec	sous la moyenne	dans la moyenne	au dessus de la moyenne
a) français	☐	☐	☐	☐
b) sciences humaines	☐	☐	☐	☐
c) mathématiques	☐	☐	☐	☐
d) sciences	☐	☐	☐	☐
Autres matières académiques: e) _____	☐	☐	☐	☐
Par exemple, informatique, f) _____	☐	☐	☐	☐
langue seconde etc g) _____	☐	☐	☐	☐

2. Votre enfant est-il dans une classe spéciale ou dans une école spéciale?

☐ non ☐ oui - quelle sorte de classe ou école spéciale? _____

3. Votre enfant a-t-il doublé une année?

☐ non ☐ oui - quelle année et pour quelle raison? _____

4. Votre enfant a-t-il déjà eu des problèmes académiques ou autres problèmes à l'école?

☐ non ☐ oui - décrivez S.V.P. _____

Quand ces problèmes ont-ils débuté?

Ces problèmes sont-ils terminés?

☐ non ☐ oui - quand? _____

XIII- Votre enfant souffre-t-il d'une maladie, d'un handicap physique ou mental?

☐ non ☐ oui - décrivez S.V.P. _____

IX- Qu'est-ce qui vous inquiète le plus au sujet de votre enfant?

X- Décrivez les plus belles qualités de votre enfant:

Voici une liste d'items qui décrivent les enfants. Pour chaque item qui décrit votre enfant actuellement ou depuis les 6 derniers mois, encerclez le 2 si l'item est toujours ou souvent vrai pour votre enfant
encerclez le 1 si l'item est assez ou quelquefois vrai pour votre enfant
encerclez le 0 si l'item n'est pas vrai pour votre enfant
Répondez à tous les items le mieux que vous le pouvez, même si quelques-uns d'entre eux ne semblent pas s'appliquer à votre enfant.

- 0 1 2 1. Fait plus jeune que son âge
0 1 2 2. A des allergies (décrivez):

0 1 2 3. Argumente beaucoup
0 1 2 4. A de l'asthme
0 1 2 5. Se comporte comme un enfant du sexe opposé
0 1 2 6. Défèque (fait caca) ailleurs que dans les toilettes
0 1 2 7. Se vante ou exagère
0 1 2 8. Ne peut se concentrer, ou garder son attention
0 1 2 9. Ne peut s'empêcher d'avoir certaines pensées, certaines obsessions (décrivez):

0 1 2 10. Ne peut rester assis ou au repos, hyperactif
0 1 2 11. Se colle avec l'adulte ou est trop dépendant
0 1 2 12. Se plaint de la solitude
0 1 2 13. Est confus ou semble être dans la lune
0 1 2 14. Pleure beaucoup
0 1 2 15. Est cruel envers les animaux
0 1 2 16. Est cruel, brutal ou mesquin envers les autres
0 1 2 17. Est rêveur ou perdu dans ses pensées
0 1 2 18. Se mutile délibérément ou a déjà fait des tentatives de suicide
0 1 2 19. Demande beaucoup d'attention
0 1 2 20. Détruit ses propres choses
0 1 2 21. Détruit des choses qui appartiennent à sa famille ou aux autres enfants
0 1 2 22. Est désobéissant à la maison
0 1 2 23. Est désobéissant à l'école
0 1 2 24. Ne mange pas bien
0 1 2 25. Ne s'entend pas bien avec les autres enfants
0 1 2 26. Ne se sent pas coupable après un mauvais comportement
0 1 2 27. Est facilement jaloux

- 0 1 2 28. Mange ou boit des choses autres que de la nourriture - ne pas inclure les friandises (décrivez):

0 1 2 29. A peur de certains animaux, situations ou lieux autre que l'école (décrivez):

0 1 2 30. A peur d'aller à l'école
0 1 2 31. A peur de penser ou de faire quelque chose de mal
0 1 2 32. Sent le besoin d'être parfait
0 1 2 33. Ressent ou se plaint que personne ne l'aime
0 1 2 34. Pense que les autres cherchent à lui nuire ou à lui faire mal
0 1 2 35. Se sent sans valeur ou inférieur
0 1 2 36. Se blesse souvent, est enclin à avoir des accidents
0 1 2 37. Se batte souvent
0 1 2 38. Se fait taquiner
0 1 2 39. Se tient avec les enfants qui font du trouble
0 1 2 40. Entend des sons ou des voix qui ne sont pas là (décrivez):

0 1 2 41. Agit sans penser, impulsif
0 1 2 42. Aime être seul
0 1 2 43. Ment ou triche
0 1 2 44. Ronge ses ongles
0 1 2 45. Est nerveux, anxieux ou tendu
0 1 2 46. A des mouvements nerveux ou des tics (décrivez):

0 1 2 47. Fait des cauchemars
0 1 2 48. N'est pas aimé des autres enfants
0 1 2 49. Est constipé, ne va pas à la selle
0 1 2 50. Est peureux ou anxieux
0 1 2 51. A le vertige, des étourdissements
0 1 2 52. Se sent souvent coupable
0 1 2 53. Mange trop
0 1 2 54. Est toujours fatigué
0 1 2 55. Est trop gros

- 0 1 2 56. A des problèmes physiques sans causes médicales connues:
- 0 1 2 a. douleurs ou mauxaises
- 0 1 2 b. maux de tête
- 0 1 2 c. nausées, maux de coeur
- 0 1 2 d. problèmes avec les yeux (décrivez):
-
- 0 1 2 e. éruptions ou problèmes de peau
- 0 1 2 f. maux d'estomac ou crampes
- 0 1 2 g. vomissements
- 0 1 2 h. autre (décrivez):
-
- 0 1 2 57. Agresse physiquement les gens
- 0 1 2 58. Joue dans son nez, avec sa peau ou autres parties de son corps (décrivez):
-
- 0 1 2 59. Joue avec ses organes génitaux en public
-
- 0 1 2 60. Joue avec ses organes génitaux fréquemment
- 0 1 2 61. Travaille mal à l'école
- 0 1 2 62. Est maladroit ou a une pauvre coordination
-
- 0 1 2 63. Préfère jouer avec des enfants plus vieux
- 0 1 2 64. Préfère jouer avec des enfants plus jeunes
- 0 1 2 65. Refuse de parler
-
- 0 1 2 66. Répète certains actes (gestes) à maintes reprises, compulsions (décrivez):
-
- 0 1 2 67. Fait des fugues
- 0 1 2 68. Crie beaucoup
- 0 1 2 69. Est peu communicatif, garde les choses pour soi
- 0 1 2 70. Voit des choses qui ne sont pas là réellement (décrivez):
-
- 0 1 2 71. Est facilement embarrassé, gêné
- 0 1 2 72. Met le feu
- 0 1 2 73. A des problèmes sexuels (décrivez):
-
- 0 1 2 74. Fait le bouffon
- 0 1 2 75. Est réservé, timide
- 0 1 2 76. Dort moins que la plupart des enfants
- 0 1 2 77. Dort plus que la plupart des enfants durant le jour ou la nuit
- 0 1 2 78. Se salit ou joue avec ses selles
- 0 1 2 79. A des problèmes de langage (décrivez):
-
- 0 1 2 80. Regarde dans le vide
- 0 1 2 81. Vole à la maison
- 0 1 2 82. Vole à l'extérieur de la maison
- 0 1 2 83. Accumule des choses dont il n'a pas besoin (décrivez):
-
-

- 0 1 2 84. A des comportements étranges (décrivez):
-
- 0 1 2 85. A des idées étranges (décrivez):
-
-
- 0 1 2 86. Est entêté, taciturne, irritable
- 0 1 2 87. Change d'humeurs ou de sentiments subitement
- 0 1 2 88. Boude souvent
- 0 1 2 89. Est méfiant, susceptible
-
- 0 1 2 90. A un langage ordurier ou obscène
- 0 1 2 91. Parle de se tuer
- 0 1 2 92. Parle ou marche en dormant (décrivez):
-
- 0 1 2 93. Parle beaucoup trop
- 0 1 2 94. Taquine souvent
- 0 1 2 95. Fait des crises de colère
- 0 1 2 96. Pense souvent aux choses sexuelles
- 0 1 2 97. Menace les gens
- 0 1 2 98. Suce son pouce ou son doigt
-
- 0 1 2 99. S'inquiète trop au sujet de l'ordre ou de la propreté
- 0 1 2 100. A des troubles du sommeil (décrivez):
-
- 0 1 2 101. Manque l'école sans raison
-
- 0 1 2 102. Est inactif, manque d'énergie
- 0 1 2 103. Est malheureux, triste, déprimé
- 0 1 2 104. Est particulièrement bruyant
-
- 0 1 2 105. Utilise des drogues ou de l'alcool sans raison médicale (décrivez):
-
-
- 0 1 2 106. Fait du vandalisme
- 0 1 2 107. Se mouille durant le jour
- 0 1 2 108. Mouille son lit
-
- 0 1 2 109. Pleurniche
- 0 1 2 110. Desirerait être du sexe opposé
- 0 1 2 111. Est retiré, ne s'implique pas avec les autres
-
- 0 1 2 112. Est inquiet, anxieux
113. Écrivez tout autre problème qu'aurait votre enfant et qui n'a pas été énuméré ici:
-
-
-
-
-

Tourette Syndrome Symptom List (Revised - TSSL)

Name of patient _____

ID# _____

Date _____

Rate each symptom by putting the appropriate number in the box each day. (Use the reverse side for any detailed comments).

0 = Not at all or symptom free. 1 = Just a little. 2 = Pretty much.		3 = Very much. 4 = Extreme. 5 = Almost always.		Rater:		☐ Patient ☐ Mother		☐ Father ☐ Other	
Date	MON	TUE	WED	THU	FRI	SAT	SUN		
SIMPLE MOTOR								SUM OF 1-11 MON - SUN 	
1. Eyeblinking									
2. Other facial tics									
3. Head jerks									
4. Shoulder jerks									
5. Arm movements									
6. Finger or hand movements									
7. Stomach jerks									
8. Kicking leg movements									
9. Tense parts of body									
10. Other:									
11. Other:									

COMPLEX MOTOR							
12. Touching part of body							
13. Touching other people							
14. Touching objects							
15. Can't start actions							
16. Hurts self							
17. Finger or hand tapping							
18. Hopping							
19. Picks at things (clothing, etc.)							
20. Copropraxia							
21. Other:							
22. Other:							

SUM OF 12-22
MON - SUN

OF SYMPTOMS 12-22
MON - SUN

SIMPLE PHONIC								SUM OF 23-28 MON - SUN		
23. Noises										
24. Grunting										
25. Throat clearing										
26. Coughing										
27. Other:										
28. Other:										

COMPLEX PHONIC								SUM OF 29-35 MON - SUN		
29. Words										
30. Repeats own words/sentences										
31. Repeats others' speech										
32. Coprolalia (obscene words)										
33. Insults (lack of inhibition)										
34. Other:										
35. Other:										

BEHAVIOR								SUM OF 36-41 MON - SUN		
36. Argumentative										
37. Poor frustration tolerance										
38. Anger, temper fits										
39. Provocative										
40. Other:										
41. Other:										

Leckman, J.F., Towbin, K.E., Ort, S.I. & Cohen, D.J. (1988). Clinical assessment of tic disorder severity. In D.J. Cohen, R.D. Bruun & J.F. Leckman (Eds), Tourette's Syndrome and Tic Disorders: Clinical Understanding and Treatment (pp. 6-78). New York, NY: John Wiley & Sons.

Liste de symptômes du syndrome de Tourette (liste révisée)

Nom du client : _____ Numéro d'identification : _____ Date: _____

Évaluez chaque symptôme en indiquant chaque jour, dans la case, le numéro correspondant. (Écrire tout commentaire détaillé au verso.)

0 = pas du tout ou aucun symptôme 1 = un peu seulement 2 = assez		3 = beaucoup 4 = extrêmement 5 = presque toujours					Personne qui remplit le questionnaire : ☐ Client ☐ Père ☐ Mère ☐ Autre	
Date	Lun.	Mar.	Mer.	Jeu.	Ven.	Sam.	Dim.	Somme de 1-11 lun. - dim. Nombre de symptômes 1-11 lun. - dim.
MOTRICITÉ SIMPLE								
1. Clignotement des yeux								
2. Autres tics du visage								
3. Secousse de la tête								
4. Secousse des épaules								
5. Mouvement des bras								
6. Mouvement des doigts ou des mains								
7. Secousse du ventre								
8. Mouvement de coup de jambe								
9. Parties tendues du corps								
10. Autre :								
11. Autre :								

MOTRICITÉ COMPLEXE									Somme de 12-22 lun. - dim. Nombre de symptômes 12-22 lun. - dim.
12. Toucher des parties du corps									
13. Toucher d'autres personnes									
14. Toucher des objets									
15. Incapable d'entreprendre une action									
16. Se fait du mal									
17. Tapotement des doigts ou des mains									
18. Sautillement									
19. Tirailleur des choses (vêtement, etc.) de façon répétitive									
20. Copropraxie :									
21. Autre :									
22. Autre :									

PHONIE SIMPLE								Somme de 23-28 lun. - dim.
23. Bruits								
24. Grognement								Nombre de symptômes 23-28 lun. - dim.
25. Racllement de la gorge								
26. Toux								
27. Autre :								
28. Autre :								

PHONIE COMPLEXE								Somme de 29-35 lun. - dim.
29. Mots								
30. Répète ses propres mots ou phrases								Nombre de symptômes 29-35 lun. - dim.
31. Répète les paroles des autres								
32. Coprolalie (mots obscènes)								
33. Insultes (manque d'inhibition)								
34. Autre :								
35. Autre :								

COMPORTEMENT								Somme de 36-41 lun. - dim.
36. Argumentateur								
37. Faible tolérance à la frustration								Nombre de symptômes 36-41 lun. - dim.
38. Colère, crise de colère								
39. Provocateur								
40. Autre :								
41. Autre :								

Leckman, J.F., Towbin, K.E., Ort, S.I. et Cohen, D.J. «Clinical assessment of tic disorder severity», dans *Tourette's Syndrome and Tic Disorders: Clinical Understanding and Treatment*, D.J. Cohen, R.D. Bruun et J.F. Leckman (édit.), New York, NY, John Wiley & Sons, 1988, p. 6-78.

Conners' Parent Rating Scale - Revised (L)

by C. Keith Conners, Ph.D.

APPENDIX F

Child's Name: _____ Gender: M F
(Circle One)

Birthdate: ____/____/____ Age: ____ School Grade: ____
Month Day Year

Parent's Name: _____ Today's Date: ____/____/____
Month Day Year

Instructions: Below are a number of common problems that children have. Please rate each item according to your child's behavior in the last month. For each item, ask yourself "How much of a problem has this been in the last month?", and circle the best answer for each one. If none, not at all, seldom, or very infrequently, you would circle 0. If very much true, or it occurs very often or frequently, you would circle 3. You would circle 1 or 2 for ratings in between. Please respond to all the items.

NOT TRUE AT ALL (Never, Seldom)	JUST A LITTLE TRUE (Occasionally)	PRETTY MUCH TRUE (Often, Quite a Bit)	VERY MUCH TRUE (Very Often, Very Frequent)
--	--	--	---

- | | | | | |
|--|---|---|---|---|
| 1. Angry and resentful | 0 | 1 | 2 | 3 |
| 2. Difficulty doing or completing homework | 0 | 1 | 2 | 3 |
| 3. Is always "on the go" or acts as if driven by a motor | 0 | 1 | 2 | 3 |
| 4. Timid, easily frightened | 0 | 1 | 2 | 3 |
| 5. Everything must be just so | 0 | 1 | 2 | 3 |
| 6. Has no friends | 0 | 1 | 2 | 3 |
| 7. Stomach aches | 0 | 1 | 2 | 3 |
| 8. Fights | 0 | 1 | 2 | 3 |
| 9. Avoids, expresses reluctance about, or has difficulties engaging in tasks that require sustained mental effort (such as schoolwork or homework) | 0 | 1 | 2 | 3 |
| 10. Has difficulty sustaining attention in tasks or play activities | 0 | 1 | 2 | 3 |
| 11. Argues with adults | 0 | 1 | 2 | 3 |
| 12. Fails to complete assignments | 0 | 1 | 2 | 3 |
| 13. Hard to control in malls or while grocery shopping | 0 | 1 | 2 | 3 |
| 14. Afraid of people | 0 | 1 | 2 | 3 |
| 15. Keeps checking things over again and again | 0 | 1 | 2 | 3 |
| 16. Loses friends quickly | 0 | 1 | 2 | 3 |
| 17. Aches and pains | 0 | 1 | 2 | 3 |
| 18. Restless or overactive | 0 | 1 | 2 | 3 |
| 19. Has trouble concentrating in class | 0 | 1 | 2 | 3 |
| 20. Does not seem to listen to what is being said to him/her | 0 | 1 | 2 | 3 |
| 21. Loses temper | 0 | 1 | 2 | 3 |
| 22. Needs close supervision to get through assignments | 0 | 1 | 2 | 3 |
| 23. Runs about or climbs excessively in situations where it is inappropriate | 0 | 1 | 2 | 3 |
| 24. Afraid of new situations | 0 | 1 | 2 | 3 |
| 25. Fussy about cleanliness | 0 | 1 | 2 | 3 |
| 26. Does not know how to make friends | 0 | 1 | 2 | 3 |
| 27. Gets aches and pains or stomachaches before school | 0 | 1 | 2 | 3 |
| 28. Excitable, impulsive | 0 | 1 | 2 | 3 |
| 29. Does not follow through on instructions and fails to finish schoolwork, chores or duties in the workplace (not due to oppositional behavior or failure to understand instructions) | 0 | 1 | 2 | 3 |
| 30. Has difficulty organizing tasks and activities | 0 | 1 | 2 | 3 |
| 31. Irritable | 0 | 1 | 2 | 3 |
| 32. Restless in the "squirmy sense" | 0 | 1 | 2 | 3 |
| 33. Afraid of being alone | 0 | 1 | 2 | 3 |
| 34. Things must be done the same way every time | 0 | 1 | 2 | 3 |
| 35. Does not get invited over to friends' houses | 0 | 1 | 2 | 3 |
| 36. Headaches | 0 | 1 | 2 | 3 |
| 37. Fails to finish things he/she starts | 0 | 1 | 2 | 3 |

Items continued on back page...

Conners' Parent Rating Scale - Revised (L)

by C. Keith Conners, Ph.D.

NOT TRUE AT ALL (Never Seldom)	JUST A LITTLE TRUE (Occasionally)	PRETTY MUCH TRUE (Often, Quite a Bit)	VERY MUCH TRUE (Very Often Very Frequent)
---	--	--	--

38. Inattentive, easily distracted	0	1	2	3
39. Talks excessively	0	1	2	3
40. Actively defies or refuses to comply with adults' requests	0	1	2	3
41. Fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities	0	1	2	3
42. Has difficulty waiting in lines or awaiting turn in games or group situations	0	1	2	3
43. Has a lot of fears	0	1	2	3
44. Has rituals that he/she must go through	0	1	2	3
45. Distractibility or attention span a problem	0	1	2	3
46. Complains about being sick even when nothing is wrong	0	1	2	3
47. Temper outbursts	0	1	2	3
48. Gets distracted when given instructions to do something	0	1	2	3
49. Interrupts or intrudes on others (e.g., butts into others' conversations or games)	0	1	2	3
50. Forgetful in daily activities	0	1	2	3
51. Cannot grasp arithmetic	0	1	2	3
52. Will run around between mouthfuls at meals	0	1	2	3
53. Afraid of the dark, animals, or bugs	0	1	2	3
54. Sets very high goals for self	0	1	2	3
55. Fidgets with hands or feet or squirms in seat	0	1	2	3
56. Short attention span	0	1	2	3
57. Touchy or easily annoyed by others	0	1	2	3
58. Has sloppy handwriting	0	1	2	3
59. Has difficulty playing or engaging in leisure activities quietly	0	1	2	3
60. Shy, withdrawn	0	1	2	3
61. Blames others for his/her mistakes or misbehavior	0	1	2	3
62. Fidgeting	0	1	2	3
63. Messy or disorganized at home or school	0	1	2	3
64. Gets upset if someone rearranges his/her things	0	1	2	3
65. Clings to parents or other adults	0	1	2	3
66. Disturbs other children	0	1	2	3
67. Deliberately does things that annoy other people	0	1	2	3
68. Demands must be met immediately — easily frustrated	0	1	2	3
69. Only attends if it is something he/she is very interested in	0	1	2	3
70. Spiteful or vindictive	0	1	2	3
71. Loses things necessary for tasks or activities (e.g., school assignments, pencils, books, tools or toys)	0	1	2	3
72. Feels inferior to others	0	1	2	3
73. Seems tired or slowed down all the time	0	1	2	3
74. Spelling is poor	0	1	2	3
75. Cries often and easily	0	1	2	3
76. Leaves seat in classroom or in other situations in which remaining seated is expected ...	0	1	2	3
77. Mood changes quickly and drastically	0	1	2	3
78. Easily frustrated in efforts	0	1	2	3
79. Easily distracted by extraneous stimuli	0	1	2	3
80. Blurts out answers to questions before the questions have been completed	0	1	2	3

QUESTIONNAIRE POUR PARENTS

Nom de l'enfant _____ Date _____
 Sexe _____ Age _____
 Votre nom _____ Parenté _____

- I. Vous trouverez ci-dessous des termes pour décrire le comportement des enfants qu'ils ont parfois. Lisez chaque énoncé attentivement et inscrivez combien vous pensez que votre enfant a été ennuyé par ce problème durant le dernier mois - 0 - PAS DU TOUT, 1 - UN PEU, 2 - ASSEZ SOUVENT, 3 - BEAUCOUP. Indiquez votre choix en encerclant le numéro approprié. PRIERE D'ENCERCLER UN SEUL NUMERO.

REPONDEZ A CHAQUE QUESTION.

Observations	Pas du tout	Un peu	Assez souvent	Beaucoup
1. Se picote les cheveux, les habits etc.	0	1	2	3
2. Impoli(e) envers les adultes.	0	1	2	3
3. Problèmes à se faire ou à garder des amis.	0	1	2	3
4. Excitable, impulsif(ve).	0	1	2	3
5. Veut tout gouverner.	0	1	2	3
6. Mâche ses vêtements, couvertures, autres.	0	1	2	3
7. Pleure facilement et souvent.	0	1	2	3
8. Cherche nuire à tout le monde.	0	1	2	3
9. Porté(e) à la rêverie.	0	1	2	3
10. N'apprend pas.	0	1	2	3
11. Agité(e) ou trop actif(ve).	0	1	2	3
12. Effrayé(e) (par les nouvelles situations, les gens, d'aller à l'école).	0	1	2	3
13. Toujours remuant.	0	1	2	3
14. Destructif(ve).	0	1	2	3
15. Raconte des histoires qui ne sont pas arrivées.	0	1	2	3
16. Timide.	0	1	2	3
17. S'attire plus d'ennuis comparé à d'autres enfants du même âge.	0	1	2	3
18. Parle différemment comparé à d'autres enfants du même âge. (Bégaye, difficile à comprendre, parle en bébé).	0	1	2	3
19. Nie avoir fait mal. Blâme les autres pour ses erreurs.	0	1	2	3
20. Querelleur(euse)	0	1	2	3

REPONDEZ A CHAQUE QUESTION.

Observations	Pas du tout	Un peu	Assez souvent	Beaucoup
21. Maussade et boudeur.	0	1	2	3
22. Vole.	0	1	2	3
23. Désobéissant(e) ou obéit avec ressentiment.	0	1	2	3
24. Se tourmente beaucoup comparativement à d'autres. (Craint d'être seul, de la maladie et de la mort).	0	1	2	3
25. Ne finit pas ce qu'il(elle) commence.	0	1	2	3
26. Facilement blessé(e) dans ses sentiments.	0	1	2	3
27. Intimide les autres (brutalité).	0	1	2	3
28. Ne peut s'empêcher de répéter une action.	0	1	2	3
29. Cruel(le).	0	1	2	3
30. Immature ou enfantin (Vaut de l'aide avec les choses qu'il(elle) devrait faire seul(e). Se colle aux parents et autres adultes. Besoin constant de réassurance)	0	1	2	3
31. Inattentif(ve), facilement distrait(e).	0	1	2	3
32. Maux de tête.	0	1	2	3
33. Humeur change vite et radicalement.	0	1	2	3
34. N'accepte pas ou n'obéit pas aux règlements et restrictions.	0	1	2	3
35. Se bat constamment.	0	1	2	3
36. Ne s'accorde pas avec ses frères et soeurs.	0	1	2	3
37. Se frustre facilement.	0	1	2	3
38. Dérange les autres enfants.	0	1	2	3
39. Malheureux(euse).	0	1	2	3
40. Problèmes avec le manger (mauvais appétit, court entre les bouchées aux repas).	0	1	2	3
41. Maux à l'estomac.	0	1	2	3
42. Problèmes de sommeil (Ne peut pas s'endormir, se lève trop de bonne heure, se réveille la nuit.	0	1	2	3
43. Autres maux et douleurs.	0	1	2	3
44. Nausée et vomissement.	0	1	2	3
45. Se sent triché au sein de sa famille.	0	1	2	3
46. Se vante, se glorifie.	0	1	2	3
47. Se laisse importuner.	0	1	2	3
48. Problèmes de défécation (Se salit, se retien de déféquer, constipation).	0	1	2	3

II. Ajoutez tout problème que vous avez avec votre enfant:

III. Combien sérieux considérez-vous le problème de votre enfant en ce moment.

☐ pas de problème ☐ problème mineur ☐ problème sérieux

IV. Indiquez les questions qui vous concernent le plus ou ceux que vous considérez le plus sérieux problèmes chez votre enfant en plaçant un cercle autour du chiffre (1 - 48) de ces questions.

V. Comment évaluez-vous le comportement de votre enfant comparé à d'autres enfants du même âge?

- ☐ beaucoup pire
- ☐ pire
- ☐ à peu près le même
- ☐ meilleur
- ☐ beaucoup meilleur

VI. Comment évaluez-vous le comportement de votre enfant depuis votre dernière visite à cette clinique?

- ☐ beaucoup pire
- ☐ pire
- ☐ à peu près le même
- ☐ meilleur
- ☐ beaucoup meilleur

ADVERSE SYMPTOMS

Date:

Subject No:

Test Session No:

Overall: (G) Good
(N) Neutral
(B) Bad

Symptoms: (A) Absent
(M) Mild
(U) Uncomfortable
(S) Severe

Symptoms	Pre-treatment	1 hour post-trmt	2 hours post-trmt	3 hours post-trmt	4 hours post-trmt	After patch removal
Overall ??						
Dizziness						
Weak/Faint						
Headache						
Ringin in Ears						
Palpitations						
Nausea						
Cramps						
Chest Pain						
Breathing Diff.						
Numbness						
Vomiting						
Other						

Physician Notes:

Name:**ID:****YGTSS Score Sheet****DOB:****Age:****Rater: A.L.H.****Sex:****Sources of Information:**

Test Session	T1	F1	T2	F2	
<u>MOTOR TICS:</u>					
Number					
Frequency					
Intensity					
Complexity					
Interference					
Total Motor Tic Score:					
<u>PHONIC TICS:</u>					
Number					
Frequency					
Intensity					
Complexity					
Interference					
Total Phonic Tic Score:					
Total Tic Score:					
Overall Impairment Rating:					
GLOBAL SEVERITY SCALE:					

Appendix

*The Yale Global Tic Severity Scale***A. Instructions**

This clinical rating scale is designed to rate the overall severity of tic symptoms across a range of dimensions (number, frequency, intensity, complexity, and interference). Use of the YGTSS requires the rater to have clinical experience with Tourette's syndrome patients. The final rating is based on all available information and reflects the clinician's overall impression for each of the items to be rated.

The style of the interview is semistructured. The interviewer should first complete the Tic Inventory (a list of motor and phonic tics present during the past week, as reported by the parent/patient, and observed during the evaluation). It is then best to proceed with questions based on each of the individual items, using the content of the anchor points as a guide.

B. Tic Inventory**1. Description of Motor Tics:** (Check motor tics present during past week)**a. Simple Motor Tics:** (Rapid, Darting, "Meaningless"):

- _____ Eye blinking
- _____ Eye movements
- _____ Nose movements
- _____ Mouth movements
- _____ Facial grimace
- _____ Head jerks/movements
- _____ Shoulder shrugs
- _____ Arm movements
- _____ Hand movements
- _____ Abdominal tensing
- _____ Leg or foot or toe movements
- _____ Other _____

b. Complex Motor Tics: (Slower, "Purposeful"):

- _____ Eye gestures or movements
- _____ Mouth movements
- _____ Facial movements or expressions
- _____ Head gestures or movements
- _____ Shoulder gestures
- _____ Arm or hand gestures
- _____ Writing tics
- _____ Dysonic postures
- _____ Bending or gyrating
- _____ Rotating
- _____ Leg or foot or toe movements
- _____ Tic-related compulsive behaviors (touching, tapping, grooming, evening-up)
- _____ Copropraxia
- _____ Self abusive behavior (describe) _____
- _____ Paroxysms of tics (displays), duration _____ seconds
- _____ Disinhibited behavior (describe)* _____
- _____ Other _____
- _____ Describe any orchestrated patterns or sequences of motor tic behaviors _____

2. Description of Phonic Tic Symptoms: (Check phonic tics present over the past week)**a. Simple Phonic Symptoms:** (Fast, "Meaningless" Sounds):

Sounds, noises: (circle: coughing, throat clearing, sniffing, grunting, whistling, animal or bird noises)
Other (list) _____

b. Complex Phonic Symptoms: (Language: Words, Phrases, Statements):

- _____ Syllables: (list) _____
- _____ Words: (list) _____
- _____ Coprolalia: (list) _____
- _____ Echolalia _____
- _____ Palalalia _____
- _____ Blocking _____
- _____ Speech atypicalities: (describe) _____
- _____ Disinhibited speech: (describe)* _____
- _____ Describe any orchestrated patterns or sequences of phonic tic behaviors _____

C. Ordinal Scales (Rate motor and phonic tics separately unless otherwise indicated).**a. Number:** Motor Score: [] Phonic Score: []**Score Description (Anchor Point)**

- 0 None
- 1 Single tic
- 2 Multiple discrete tics (2-5)
- 3 Multiple discrete tics (>5)
- 4 Multiple discrete tics plus at least one orchestrated pattern of multiple simultaneous or sequential tics where it is difficult to distinguish discrete tics.
- 5 Multiple discrete tics plus several (>2) orchestrated patterns of multiple simultaneous or sequential tics where it is difficult to distinguish discrete tics.

b. Frequency: Motor Score: [] Phonic Score: []**Score Description (Anchor Point)**

- 0 None. No evidence of specific tic behaviors.
- 1 Rarely. Specific tic behaviors have been present during previous week. These behaviors occur infrequently, often not on a daily basis. If bouts of tics occur, they are brief and uncommon.
- 2 Occasionally. Specific tic behaviors are usually present on a daily basis, but there are long tic-free intervals during the day. Bouts of tics may occur on occasion and are not sustained for more than a few minutes at a time.
- 3 Frequently. Specific tic behaviors are present on a daily basis. Tic free intervals as long as 3 hours are not uncommon. Bouts of tics occur regularly but may be limited to a single setting.
- 4 Almost Always. Specific tic behaviors are present virtually every waking hour of every day, and periods of sustained tic behaviors occur regularly. Bouts of tics are common and are not limited to a single setting.
- 5 Always. Specific tic behaviors are present virtually all the time. Tic-free intervals are difficult to identify and do not last more than 5 to 10 minutes at most.

*Do not include this item in rating the ordinal scales.

- c. **Intensity** Motor Score: [] Phonic Score: []
- Score Description (Anchor Point)**
- 0 *Absent*
- 1 *Minimal intensity*, tics not visible or audible (based solely on patient's private experience) or tics are less forceful than comparable voluntary actions and are typically not noticed because of their intensity.
- 2 *Mild intensity*, tics are not more forceful than comparable voluntary actions or utterances and are typically not noticed because of their intensity.
- 3 *Moderate intensity*, tics are more forceful than comparable voluntary actions but are not outside the range of normal expression for comparable voluntary actions or utterances. They may call attention to the individual because of their forceful character.
- 4 *Marked intensity*, tics are more forceful than comparable voluntary actions or utterances and typically have an "exaggerated" character. Such tics frequently call attention to the individual because of their forceful and exaggerated character.
- 5 *Severe intensity*, tics are extremely forceful and exaggerated in expression. These tics call attention to the individual and may result in risk of physical injury (accidental, provoked, or self-inflicted) because of their forceful expression.

- d. **Complexity:** Motor Score: [] Phonic Score: []
- Score Description (Anchor Point)**
- 0 *None*, if present, all tics are clearly "simple" (sudden, brief, purposeless) in character.
- 1 *Borderline*, some tics are not clearly "simple" in character.
- 2 *Mild*, some tics are clearly "complex" (purposive in appearance) and mimic brief "automatic" behaviors, such as grooming, syllables or brief meaningful utterances such as "ah huh," "hi," that could be readily camouflaged.
- 3 *Moderate*, some tics are more "complex" (more purposive and sustained in appearance) and may occur in orchestrated bouts that would be difficult to camouflage but could be rationalized or "explained" as normal behavior or speech (picking, tapping, saying "you bet" or "honey," brief echolalia).
- 4 *Marked*, some tics are very "complex" in character and tend to occur in sustained orchestrated bouts that would be difficult to camouflage and could not be easily rationalized as normal behavior or speech because of their duration and/or their unusual, inappropriate, bizarre, or obscene character (a lengthy facial contortion, touching genitals, echolalia, speech atypicalities, longer bouts of saying "what do you mean" repeatedly, or saying "fu" or "sh").
- 5 *Severe*, some tics involve lengthy bouts of orchestrated behavior or speech that would be impossible to camouflage or successfully rationalize as normal because of their duration and/or extremely unusual, inappropriate, bizarre, or obscene character (lengthy displays or utterances often involving copropraxia, self-abusive behavior, or coprolalia).

- e. **Interference:** Motor Score: [] Phonic Score: []
- Score Description (Anchor Point)**
- 0 *None*
- 1 *Minimal*, when tics are present, they do not interrupt the flow of behavior or speech.
- 2 *Mild*, when tics are present, they occasionally interrupt the flow of behavior or speech.

- 3 *Moderate*, when tics are present, they frequently interrupt the flow of behavior or speech.
- 4 *Marked*, when tics are present, they frequently interrupt the flow of behavior or speech, and they occasionally disrupt intended action or communication.
- 5 *Severe*, when tics are present, they frequently disrupt intended action or communication.

f. **Impairment** Overall Impairment: [] (Rate Overall Impairment for Motor and Phonic Tics):

Score Description (Anchor Point)

- 0 *None*
- 10 *Minimal*, tics associated with subtle difficulties in self-esteem, family life, social acceptance, or school or job functioning (infrequent upset or concern about tics vis à vis the future; periodic, slight increase in family tensions because of tics; friends or acquaintances may occasionally notice or comment about tics in an upsetting way).
- 20 *Mild*, tics associated with minor difficulties in self-esteem, family life, social acceptance, or school or job functioning (episodes of dysphoria, periodic distress and upheaval in the family, frequent teasing by peers or episodic social avoidance, periodic interference in school or job performance because of tics).
- 30 *Moderate*, tics associated with some clear problems in self-esteem, family life, social acceptance, or school or job functioning (episodes of dysphoria, periodic distress and upheaval in the family, frequent teasing by peers or episodic social avoidance, periodic interference in school or job performance because of tics).
- 40 *Marked*, tics associated with major difficulties in self-esteem, family life, social acceptance, or school or job functioning.
- 50 *Severe*, tics associated with extreme difficulties in self-esteem, family life, social acceptance, or school or job functioning (severe depression with suicidal ideation, disruption of the family [separation/divorce, residential placement], disruption of social ties—severely restricted life because of social stigma and social avoidance, removal from school or loss of job).

D. Score Sheet.

Name _____ Date _____
 DOB _____ Sex _____
 Sources of Information _____

Raters _____

Motor Tics:

Number	[]
Frequency	[]
Intensity	[]
Complexity	[]
Interference	[]
Total Motor Tic Score	[]

Phonic Tics:

Number	[]
Frequency	[]
Intensity	[]
Complexity	[]
Interference	[]
Total Phonic Tic Score	[]

Overall Impairment Rating

Global Severity Score (Motor + Phonic + Impairment)	[]
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Children's Hospital of Eastern Ontario
Hôpital pour enfants de l'est de l'Ontario

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ROYAL OTTAWA HOSPITAL
HÔPITAL ROYAL OTTAWA

A Division of the Royal Ottawa Health Care Group / Une division des services de santé Royal Ottawa

Clinical and Attentional Effects of Acute Nicotine Treatment in Tourette's Disorder

Child / Adolescent Information Sheet (Ages 9-16)

You have been asked to take part in this study because you have Tourette's Disorder and we are testing a new treatment for Tourette's. Research has shown that when nicotine is added to your usual Tourette's medication (e.g., Haldol, Orap or Risperdal) it helps the medication work better. With many of the children and adolescents it has been tried with, it has reduced their tics and improved their attention more than when they took their Tourette's medication alone.

You will need to come to the Royal Ottawa Hospital 4 more times. Each time you come you will be asked to describe your tics to the researcher. So that we can count your tics, the interview with the researcher will be videotaped. During the visit you will also do a very easy test on the computer. Small sensors will be placed on your head during the computer test to see how your brain is responding to the nicotine. On 2 of the 4 visits a patch, like a small bandaid, will be put on your arm for a few hours. The patch will contain either a small amount of nicotine or it will contain nothing at all. You won't be able to tell the difference and we will not know which you received on which visit until the end of the study. We will also ask your parent(s) to fill in a tic checklist and two behaviour checklists.

No benefit can be promised to you from your participation in this study. However, when nicotine is added to your Tourette's medication, it may help to reduce your tics and/or increase your ability to concentrate. Some, but not all, children and adolescents with Tourette's who have tried the nicotine patch have said that it made them feel uncomfortable. The most common complaints were that the nicotine patch made their skin itch, their stomach upset or gave them a headache while the patch was on their arm. There is very little risk of becoming addicted to cigarettes from one nicotine patch.

Your participation is completely voluntary and you have the right to withdraw from the study at any time without having your Tourette's treatment affected in any way. If you have any problems or questions about the study, you can phone Anne Howson at 722-6521 ext. 6558.

We appreciate your taking part in the study as knowledge gained from this research project may benefit yourself and others with Tourette's Disorder in the future.



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ROYAL OTTAWA HOSPITAL
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INFORMED CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY

Date: May 23, 1997

Title of Study: Clinical and Attentional Effects of Acute Nicotine Treatment in Tourette's Disorder

Principal Investigator: A. Howson (PhD Student - Department of Psychology, University of Ottawa)

Associate Investigators: A. Boisjoli, MD, M. Jaworski, MD
V. Ilivitsky, MD

Study Supervisor: V. Knott, D.Phil.

BACKGROUND TO STUDY

Motor and vocal tics associated with Tourette's Disorder (TD) are often treated with dopamine blocking agents (e.g. Haldol, Orap). Dopamine is a common brain chemical involved in carrying nerve impulses. Dopamine has been shown to have an important role in controlling many aspects of physiology, including motor behaviour. In addition to tics, children and adolescents with TD can also have a number of psychological problems including difficulty in focusing and sustaining attention. These difficulties can be part of TD itself or they can be the result of the medication used to treat TD. The last situation can occur when standard doses of dopamine blocking medications do not effectively control the motor and vocal tics associated with TD and therefore require the use of higher doses. It is these higher doses which often induce sedation and a decline in attention in sustained, effort-demanding situations (e.g. such as in the classroom).

Nicotine has been shown to activate the brain and preliminary TD research has shown that when nicotine is given in combination with dopamine blocking medication it appears to result in a greater reduction of motor and vocal tics than when the neuroleptic is given alone. There is some indication that effects resulting from a single nicotine patch, given in combination with a dopamine blocking agent, may last for up to 2 weeks on average.

In addition, in normal volunteers and in people with disorders such as Parkinson's disease, schizophrenia and Alzheimer's disease, nicotine on its own has been shown to improve human performance on a wide range of cognitive tasks when it is inhaled, administered orally (by tablet or gum) or absorbed through the skin with a nicotine patch. Brain imaging research has shown that nicotine activates regions of the brain which control attention, thereby resulting in an increased ability to focus and sustain attention.

OBJECTIVE OF STUDY

This research project developed from the following two findings:

- 1) nicotine combined with dopamine blocking medication has been shown to reduce motor and vocal tics to a greater extent than when the dopamine blocking medications are given alone and**
- 2) nicotine administration alone has been shown to improve aspects of attention in a number of neuropsychiatric disorders such as schizophrenia and Alzheimer's disease.**

This study will therefore attempt to examine the short- and long-term effects of a single transdermal nicotine patch, given as a supplement to your child's usual TD medication: (e.g. Haldol, Orap), on the clinical symptoms of motor and vocal tics as well as on laboratory measures and clinical ratings of attention.

PROCEDURES OF STUDY

Orientation Session		
week 1	Test Session #1	(6hours)
	<i>-one hour testing*</i> <i>-treatment (placebo or nicotine)</i> <i>-waiting period (4 hours)</i> <i>-one hour testing*</i>	
week 2	Follow-up #1	(1 hour)
	<i>- one hour testing*</i>	
week 8	Test Session #2	(6 hours)
	<i>-one hour testing*</i> <i>-treatment (nicotine or placebo)</i> <i>-waiting period (4 hours)</i> <i>-one hour testing*</i>	
week 9	Follow-up #2	(1 hour)
	<i>- one hour testing*</i>	
<i>*one hour testing: tic inventory interview and computer task</i>		

This study will require that your child attend the laboratory for a 1 hour orientation session, two test sessions of 6 hours each and a 1 hour follow-up session 1 week after each test session (for a total of 5 visits). Test sessions will be separated by 2 months. Your involvement in this study, as a parent/guardian will be limited to the completion of three rating scales, two of which will be completed during each visit. You will be asked

to complete one rating scale assessing your child's tics over the previous week and two other rating scales assessing various aspects of your child's behaviour. One of the behaviour rating scales will be given during each visit and will ask you to assess your child's behaviour for the previous week.

During each laboratory test session, attention will be assessed physiologically and behaviorally by placing sensors on your child's scalp to record their brain waves during an 11 minute computerized task. Ten sensors will be painlessly applied with a special gel. The sensors placed on your child's scalp and skin may cause a mild and temporary irritation and redness of the skin which will disappear in a few hours. Following the sensor application, your child will be asked to watch a computer screen and to press a button whenever a particular number (stimulus) appears on the screen.

The small scalp-recorded brain wave responses, which occur each time a number appears on the screen, are called event-related potentials (ERPs). The size (amplitude) and the timing (latency) of these potentials provide us with information about how efficiently the attention centres of the brain are working and together with measures of your child's behavioural performance (i.e. reaction times and response accuracy), they will be used to assess the effect of nicotine added to the usual dopamine blocking medication prescribed to your child. The brain wave monitoring for the ERPs is very similar to electroencephalogram or EEG monitoring carried out in general hospitals except that it uses a computer to record and analyze the brain waves.

In the first test session, measures of brain function and behavioural performance will be taken during the tasks which will be carried out before and 4 hours after the administration of a transdermal patch. The patch will either contain 7mg of nicotine (the most common dose used in children and adolescents in TD research to date) or the patch will be a placebo and will contain no nicotine. Which subjects receive the nicotine patch and which subjects receive the placebo patch will be randomized and "double blind" so that neither you nor the experimenter will know which your child is receiving.

Your child will also be videotaped for 15 minutes before and again 4 hours after receiving the transdermal patch in order for the researchers to measure the number, type and intensity of tics your child has. While your child is being videotaped he/she will be asked to describe his or her tics to the examiner (5 minutes), then to sit and relax (5 minutes) and then to listen to and repeat some numbers and to copy some symbols onto a sheet of paper (5 minutes). During the 4 hour waiting interval after the patch has been applied, your child will be able to read or watch a video.

One week after the first test session you will be asked to return to the laboratory. During this second session your child will not be administered any nicotine but your child's brain waves will be recorded again while he/she carries out the same computerized task. Your child will also be videotaped for 15 minutes in the same way as for the first test session.

Two months after the first test session you will be asked to return to the laboratory to complete the second phase of the study, which will involve laboratory testing and a one week follow-up session. All the procedures will be the same as those during the first test and follow-up session. The only difference will be that your child will receive the treatment (i.e. either the placebo patch or the nicotine patch) that he or she did not receive in the first phase of the study. Again neither the subject nor the experimenter will know who received what and when until after the study is completed.

POTENTIAL BENEFITS

No benefit can be promised to you from your participation in this study. However, if nicotine given in combination with your child's existing drug treatment proves to have advantages over the current treatment for TD, your child's participation may be beneficial to him/her self and any other individuals with TD in the future.

POSSIBLE RISKS INVOLVED

The risks are minimal. The nicotine patch is frequently used in adults as a treatment to

help smokers stop smoking. The 7 mg nicotine patch, administered on a single occasion, raises blood nicotine to levels slightly lower than those obtained when smoking a single cigarette. Reviewing the studies of nicotine given in combination dopamine blocking medication, acute test doses of nicotine have been administered as a transdermal nicotine patch to a total of 39 TD patients and in the form of chewing gum to a total of 36 TD patients. Of the 77 TD cases reported on thus far, 55 of them were children and adolescents between the ages of 6 and 18.

The main side effects which may be experienced with the transdermal nicotine patch include nausea, salivation, abdominal pain, vomiting, diarrhea, cold sweat, headaches, dizziness, disturbed hearing and vision, mental confusion, weakness, fainting, respiratory difficulty and increased, weak and irregular heart rate. It should be realized that while this list of side effects experienced by some patients is quite extensive, they are temporary (usually not lasting more than 24 hours) and are more typically seen in subjects who use the patch on a daily basis. The frequency of appearance of these symptoms tends to be higher in non-smokers who have not built-up a tolerance to nicotine.

Compared to nicotine inhaled from cigarettes, transdermal nicotine applied in patch form as in this study, has a very low probability of inducing addiction. There are three reasons for a low addiction potential: 1) nicotine is absorbed very slowly from the patch compared to nicotine absorbed from cigarettes and fast, rather than slow, absorption is characteristic of addictive drugs 2) lower blood levels of nicotine are obtained with the patch as compared to cigarettes and 3) the nicotine patch is only being administered once while cigarettes are smoked frequently through the day and over time.

OTHER INFORMATION

Confidentiality: Information will be coded and your child's privacy will be protected. Any scientific publications from this work will be designed so that your child's anonymity will be preserved.

Problems or Questions: The principal investigator is Anne Howson. You may contact Ms. Howson at 722-6521, ext. 6558, if you have any problems or questions about the study. The address of the Royal Ottawa Hospital is 1145 Carling Avenue, Ottawa, Ontario, K1Z 7K4. You may also contact Drs. Bolsjoli and Jaworski at the Tourette Syndrome Clinic located in The Child and Family Psychiatric Unit, 311 McArthur, Suite 200, Vanier, Ontario K1L 8M3. The phone number is 737-8325.

You may contact the Chair of the Research Ethics Committee at the Children's Hospital of Eastern Ontario (CHEO) for information regarding patient's rights in research studies (tel.# 738-3272); however, this person cannot provide any medical information with regard to this study.

Participation: Your participation is entirely voluntary and it is understood and agreed that there will be no monetary remuneration or other consideration payable to you or to your child. You have the right to withdraw from the study at any time without any bearing on your treatment. Your doctor or the study doctor may also withdraw your child from the study at any time if they feel it is not in your best interest to continue with the study procedures. We appreciate your involvement as knowledge gained from this research project may benefit individuals with Tourette's Disorder in the future.

Please keep a copy of this document for your personal records.

**ROYAL OTTAWA HOSPITAL
HÔPITAL ROYAL OTTAWA**

A Division of the Royal Ottawa Health Care Group / Une division des services de santé Royal Ottawa

CONSENT FORM

Patient Name: _____ **Date of Birth:** _____

**Study Name: Clinical and Attentional Effects of Acute Nicotine Treatment in
Tourette's Disorder**

I have read and understood the Informed Consent Statement for this study and all my questions have been answered. I understand that this is a consent to participate in a research study and I also understand that my child's clinical treatment will continue to be carried out at the Tourette Syndrome Clinic. I understand and agree that there will be no monetary remuneration or other consideration payable to me or to my child. I voluntarily consent to allow my child to participate in this study and I understand that I can withdraw consent at any time without affecting the treatment received by my child from the Tourette Syndrome Clinic.

LEGAL GUARDIAN'S CONSENT

(for patients under 16 years)

Legal Guardian's Name: _____ **Relationship:** _____

Legal Guardian's Signature: _____ **Date:** _____

Witness: _____ **Date:** _____

Investigator: _____ **Date:** _____

INFORMED ASSENT

(to be signed by patients under 16 years)

I, _____ understand what is required for the study and agree to take part.

Patient Signature: _____ **Date:** _____



Children's Hospital of Eastern Ontario
Hôpital pour enfants de l'est de l'Ontario

401 BAYVIEW, OTTAWA, ONT. K1H 8L1 TELEPHONE (613) 737-7000

CONSENT FORM

Patient Name: _____ **Date of Birth:** _____

Study Name: Clinical and Attentional Effects of Acute Nicotine Treatment in Tourette's Disorder

I have read and understood the Informed Consent Statement for this study and all my questions have been answered. I understand that this is a consent to participate in a research study and I also understand that my child's clinical treatment will continue to be carried out at the Tourette Syndrome Clinic. I understand and agree that there will be no monetary remuneration or other consideration payable to me or to my child. I voluntarily consent to allow my child to participate in this study and I understand that I can withdraw consent at any time without affecting the treatment received by my child from the Tourette Syndrome Clinic.

LEGAL GUARDIAN'S CONSENT

Legal Guardian's Name: _____ **Relationship:** _____

Legal Guardian's Signature: _____ **Date:** _____

Witness: _____ **Date:** _____

Investigator: _____ **Date:** _____

INFORMED ASSENT

I, _____ understand what is required for the study and agree to take part.

Patient Signature: _____ **Date:** _____



Children's Hospital of Eastern Ontario
Hôpital pour enfants de l'est de l'Ontario

401 Smyth, OTTAWA, ONT K1H 8L1 TÉLÉPHONE (613) 737-7600



ROYAL OTTAWA HOSPITAL
HÔPITAL ROYAL OTTAWA

A Division of the Royal Ottawa Health Care Group / Une division des services de santé Royal Ottawa

Effets cliniques et attentionnels du traitement aigu à la nicotine dans le traitement du syndrome de Tourette

Feuille d'information pour les enfants et les adolescents (âgés de 8 à 16 ans)

Nous vous avons demandé de participer à cette expérience parce que vous avez la maladie de Tourette et que nous voulons tester un nouveau traitement pour cette maladie. Les recherches ont montré que les médicaments que vous prenez normalement (par exemple, Haldol, Orap ou Risperdal) fonctionnent mieux lorsqu'on y ajoute de la nicotine. Beaucoup des enfants et des adolescents qui ont essayé ce nouveau traitement ont dit qu'ils avaient moins de tics et une meilleure attention avec le nouveau traitement que quand ils prenaient leurs médicaments sans nicotine.

Pour participer à cette expérience, il vous faudra venir à l'Hôpital Royal d'Ottawa 4 fois. Chaque fois, la personne qui va vous rencontrer va vous demander de décrire vos tics. Nous allons aussi enregistrer votre conversation avec cette personne sur une vidéo parce que nous voulons compter vos tics. Pendant votre visite, nous allons vous demander de faire un test très facile sur l'ordinateur. Pendant ce test, nous allons placer des détecteurs sur votre tête pour voir comment votre cerveau réagit à la nicotine que nous avons ajoutée à vos médicaments. Pendant 2 des 4 visites, nous allons aussi placer sur votre bras, pendant quelques heures, un timbre qui ressemble à une petite bande adhésive. Le timbre contiendra une petite quantité de nicotine ou contiendra rien du tout. Vous ne pourrez pas dire la différence. Nous ne pourrions pas dire non plus, lors de telle ou telle visite, si vous avez reçu le timbre qui contient de la nicotine ou un timbre qui n'en contient pas. Il faudra attendre à la toute fin de l'expérience pour le savoir. On va aussi donner une liste à vos parents pour qu'ils notent vos comportements.

On ne peut pas vous garantir qu'il y a des avantages pour vous si vous participez à notre expérience. Mais, quand on ajoute de la nicotine à vos médicaments pour la maladie de Tourette, il est possible que vous aurez moins de tics et que vous pourrez mieux vous concentrer. Parmi les enfants et adolescents qui ont essayé le traitement avec la nicotine, il y en a certains, mais pas tous, qui nous ont dit que le traitement n'était pas toujours confortable. Le plus souvent, ils se sont plaints que la peau leur grattait avec le timbre, que le timbre leur donnait mal à la tête ou qu'ils avaient l'estomac dérangé. Il y a très peu de chances que vous pourriez développer une accoutumance à la cigarette à partir d'un timbre de nicotine.

C'est strictement à vous de décider si vous voulez participer à cette expérience et vous pouvez arrêter de participer n'importe quand sans que cela n'affecte votre traitement pour votre maladie de Tourette. Si vous avez des problèmes ou des questions au sujet de cette expérience, vous pouvez téléphoner à Anne Howson au numéro 722-6521 (poste 6558). Nous apprécions que vous participiez à cette expérience. Ce que nous allons apprendre à partir de cette expérience pourrait vous aider et aider d'autres personnes qui ont la maladie de Tourette dans le futur.



CONSENTEMENT ÉCLAIRÉ À PARTICIPER À UN PROJET DE RECHERCHE CLINIQUE

Date: Le 23 mai 1998

Titre du projet de recherche: Les effets cliniques et attentionnels du traitement aigu à la nicotine dans le traitement du syndrome de Tourette

Chercheur principal: A. Howson (doctorat en cours, Département de psychologie, Université d'Ottawa)

Chercheurs associés: A. Boisjoli, MD
M. Jaworski, MD
V. Ilivitsky, MD

Superviseur du projet: V. Knott, D. Phil.

RENSEIGNEMENTS GÉNÉRAUX SUR LE PROJET

Les tics moteurs et verbaux associés au Syndrome de Tourette (ST) sont souvent traités par des médicaments neuroleptiques ou des médicaments qui bloquent la transmission de la dopamine. La dopamine est un produit chimique courant du cerveau participant à la transmission nerveuse. On a démontré que la dopamine jouait un rôle important pour contrôler de nombreux aspects de la physiologie, y compris le comportement moteur. En plus de tics, les enfants et les adolescents atteints du syndrome de Tourette peuvent aussi présenter un certain nombre de problèmes psychologiques, y compris une difficulté à concentrer et à soutenir leur attention. Ces difficultés peuvent faire partie du ST lui-même ou peuvent être provoquées par le médicament utilisé pour traiter le ST. Lorsque la difficulté est due au médicament utilisé pour traiter le ST, il est possible que les doses normales de neuroleptique ne contrôlent pas suffisamment les tics moteurs et vocaux associés au ST et qu'il faut donc utiliser des doses plus fortes. C'est souvent ces doses plus fortes qui causent l'effet calmant et qui peut faire que votre attention diminue dans une situation qui demande un effort pendant un certain temps, comme dans une salle de classe par exemple.

Les recherches ont montré que la nicotine active le cerveau. Aussi, d'autres recherches préliminaires sur le ST ont montré que quand on donne la nicotine en combinaison avec un neuroleptique, il semble y avoir moins de tics moteurs et vocaux que quand le neuroleptique est donné seul. Il y a certaines indications que les effets causés par un seul timbre de nicotine, donné en même temps qu'un neuroleptique, pourraient durer jusqu'à 2 semaines, en moyenne.

De plus, chez des volontaires normaux et des personnes qui ont des maladies comme la maladie de Parkinson, la schizophrénie et la maladie d'Alzheimer, on a trouvé que la nicotine seule est capable d'améliorer la capacité de faire plusieurs tâches cognitives quand elle est inhalée, pris oralement (sous forme de comprimé ou de gomme à mâcher) ou absorbée par la peau au moyen d'un timbre de nicotine. Les recherches en imagerie cérébrale ont montré que la nicotine active les régions de notre cerveau qui contrôlent l'attention, ce qui nous aiderait à nous concentrer et à soutenir notre attention.

OBJECTIF DU PROJET

Ce projet de recherche découle de deux découvertes:

1. On a démontré que la nicotine combinée aux neuroleptiques réduisait davantage les tics moteurs et verbaux que les neuroleptiques donnés seuls;
2. On a démontré que l'administration de nicotine seule améliorait des aspects de l'attention pour un certain nombre de troubles neuropsychiatriques, comme la schizophrénie et la maladie d'Alzheimer.

Ce projet de recherche va donc examiner les effets à long et à court terme de l'application unique d'un timbre transdermique à la nicotine, donné en plus du régime habituel de neuroleptique de votre enfant, sur les symptômes cliniques de tics moteurs et vocaux, ainsi que sur les mesures faites en laboratoire et l'observation clinique de l'attention.

DESCRIPTION DU PROJET

Dans le cadre de ce projet de recherche, votre enfant viendra à une séance de pratique au laboratoire à deux séances de tests et à une séance de suivi, une semaine après chaque

séance de tests (5 visites au total). Les séances de tests seront séparées par 2 mois. Votre participation à ce projet de recherche, en tant que parent/tuteur, sera limitée à compléter trois échelles d'évaluation. Pendant chaque visite, vous complétez deux échelles évaluant divers aspects du comportement de votre enfant et un inventaire des tics.

Pendant chaque séance de tests de laboratoire, l'attention sera évaluée sur les plans de la physiologie et du comportement, au moyen de sondes placées sur le cuir chevelu de votre enfant pour enregistrer les ondes cérébrales, pendant une tâche informatisée de 10 minutes. On demandera à votre enfant de regarder un écran d'ordinateur et de presser sur un bouton à chaque fois qu'un chiffre particulier (stimulus) apparaîtra à l'écran.

Les petites réactions des ondes du cerveau enregistrées à partir du cuir chevelu et qui prennent place chaque fois qu'un chiffre apparaît sur l'écran, sont appelées «potentiels reliés aux événements». La grosseur (amplitude) et le moment de l'apparition (latence) de ces potentiels nous disent si les centres d'attention du cerveau fonctionnent efficacement. Cette information, en plus de la mesure du rendement comportemental de votre enfant (temps de réaction et exactitude de la réaction), servira à évaluer l'effet de la nicotine qui a été ajoutée au médicament neuroleptique habituel prescrit à votre enfant.

Pendant la première séance de tests, on mesurera le fonctionnement du cerveau et le rendement comportemental pendant des tâches effectuées avant et 4 heures après l'application d'un timbre transdermique. Le timbre contient soit 7 mg de nicotine (la dose la plus courante utilisée jusqu'à présent chez les enfants et les adolescents dans les projets de recherche sur le syndrome de Tourette) ou le timbre sera un placebo qui ne contiendra pas de nicotine. Quels sujets recevront le timbre de nicotine et quels sujets recevront le timbre placebo sera décidé au hasard, à double insu, pour que ni vous ni le chercheur ne sachiez ce que votre enfant recevrait.

Votre enfant sera aussi filmé par caméra vidéo 15 minutes avant et 4 heures après avoir reçu le timbre transdermique, pour que les chercheurs puissent mesurer le nombre, le type et l'intensité des tics de votre enfant. Pendant que votre enfant sera filmé, on lui demandera de décrire ses tics à l'examineur (5 minutes), puis de se relaxer, assis (5 minutes), et ensuite d'écouter et de répéter certains chiffres et de recopier des symboles sur une feuille de papier (5 minutes). Pendant l'intervalle d'attente de 4 heures après la pose du timbre, votre enfant aura le droit de lire ou de regarder des documentaires vidéos.

Une semaine après la première séance de tests, on vous demandera de revenir au laboratoire. Pendant cette deuxième séance, on ne donnera pas de nicotine à votre enfant, mais les ondes cérébrales de votre enfant seront enregistrées de nouveau pendant qu'il exécutera la même tâche informatisée. Votre enfant sera aussi filmé pendant 15 minutes de la même manière que pendant la première séance de tests.

Deux mois après la première séance de tests, on vous demandera de revenir au laboratoire pour la deuxième phase du projet de recherche, comportant des tests de laboratoire et une séance de suivi d'une semaine. Toutes les interventions seront les mêmes que pendant la première séance de tests et de suivi. La seule différence sera que votre enfant recevra le traitement (soit le timbre placebo soit le timbre à la nicotine) qu'il n'avait pas reçu pendant la première phase du projet. Une fois de plus, ni le sujet ni le chercheur ne sauront avant la fin de l'étude ce qui a été donné et quand.

AVANTAGES POSSIBLES

Nous ne pouvons vous garantir aucun avantage découlant de votre participation à ce projet de recherche. Cependant, si la nicotine donnée en combinaison avec le médicament existant de votre enfant semble donner de meilleurs résultats que le traitement actuel du syndrome de Tourette, la participation de votre enfant pourrait lui être bénéfique et être bénéfique aux autres personnes qui auront le syndrome de Tourette à l'avenir.

RISQUES POSSIBLES

Les risques sont minimes. Le timbre à la nicotine est fréquemment utilisé chez les adultes, comme traitement pour aider les fumeurs à renoncer au tabac. Le timbre de 7 mg de nicotine, administré une seule fois, fait monter le niveau sanguin de nicotine un peu moins que si la personne fumait une seule cigarette. Si on passe en revue les études sur la nicotine données en combinaison avec des neuroleptiques (agents bloquant la dopamine), on voit que des doses de test élevées de nicotine ont été administrées par timbre transdermique de nicotine à un total de 39 patients présentant un syndrome de Tourette et sous la forme de gomme à mâcher à 36 patients. Sur les 77 cas de ST signalés jusqu'à présent, 55 d'entre eux étaient des enfants et des adolescents entre les âges de 6 et 18 ans.

Les effets secondaires principaux signalés avec le timbre transdermique de nicotine sont la

nausée, la salivation, la douleur abdominale, les vomissements, la diarrhée, les sueurs froides, les maux de tête, les étourdissements, les troubles de l'audition et de la vision, la confusion mentale, la faiblesse, les évanouissements, les difficultés respiratoires et les battements cardiaques plus rapides, faibles et irréguliers. Il faut savoir que, bien que cette liste des effets secondaires signalés par certains patients soit assez longue, les effets sont temporaires (ne durant généralement pas plus de 24 heures) et sont plus typiquement vus chez les sujets qui utilisent le timbre quotidiennement. La fréquence d'apparence de ces symptômes tend à être plus élevée chez les non fumeurs qui n'ont pas acquis de tolérance à la nicotine.

Par comparaison avec la nicotine inhalée quand on fume une cigarette, la nicotine transdermique utilisée sous forme de timbre, comme c'est le cas dans ce projet de recherche, a très peu de chances de causer l'accoutumance. Les faibles possibilités de développer une accoutumance sont dues à trois raisons : 1) La nicotine est absorbée très lentement à partir du timbre par comparaison avec la nicotine absorbée quand on fume des cigarettes. Aussi, c'est l'absorption rapide, plutôt que l'absorption lente, qui est caractéristique des médicaments accoutumants; 2) Les niveaux de nicotine dans le sang sont plus faibles avec le timbre qu'avec les cigarettes et 3) Le timbre de nicotine n'est administré qu'une seule fois, alors que quand on fume, on fume des cigarettes fréquemment pendant la journée, sur une longue période.

La surveillance des ondes cérébrales dans le cadre des potentiels reliés aux événements est très semblable à la surveillance par EEG (électro-encéphalogramme) effectuée dans des hôpitaux généraux, à part le fait qu'on utilise un ordinateur pour enregistrer et analyser les ondes cérébrales. Les sondes placées sur votre cuir chevelu et votre peau pourraient causer une irritation légère et temporaire et une rougeur de la peau, qui disparaîtront en quelques heures.

AUTRES INFORMATIONS

Confidentialité: Les informations seront codées et l'anonymat de votre enfant sera préservé. Toute publication scientifique découlant de ce travail préservera l'anonymat de votre enfant.

Problèmes ou questions: La chercheuse principale est Anne Howson. Vous pouvez contacter Mme. Howson au 722-6521, poste 6558, si vous avez des problèmes ou des questions à poser sur le projet. L'adresse de l'Hôpital Royal Ottawa est le 1145, avenue Carling, Ottawa (Ontario) K1Z 7K4. Vous pouvez aussi contacter les Drs Boisjoli et Jaworski à la clinique de Tourette située à l'Unité psychiatrique de l'enfant et des familles, 311, chemin McArthur, suite 200, Vanier, ON (738-6990).

You may contact the Chair of the Research Ethics Committee at the Children's Hospital of Eastern Ontario (CHEO) for information regarding patient's rights in research studies (tel.# 738-3272); however, this person cannot provide any medical information with regard to this study.

Participation: Votre participation est entièrement volontaire, et vous avez le droit de vous retirer du projet à n'importe quel moment, sans porter préjudice à votre traitement. Votre médecin ou le médecin du projet pourrait aussi retirer votre enfant de l'étude à n'importe quel moment s'il pense que ce n'est pas dans votre intérêt de continuer à y participer. Nous apprécions votre participation, car les connaissances obtenues grâce à ce projet pourraient bénéficier à l'avenir aux personnes ayant le syndrome de Tourette.

Veillez conserver une copie de ce document dans vos dossiers personnels.

FORMULAIRE DE CONSENTEMENT

Nom du patient: _____ Date de naissance: _____

Nom du projet: **Les effets cliniques et attentionnels du traitement aigu à la nicotine dans le traitement du syndrome de Tourette**

J'ai lu et compris le texte du consentement éclairé à cette étude, et on a répondu à toutes mes questions. Je consens volontairement à ce que mon enfant participe à ce projet de recherche et je comprends que je peux l'en retirer à n'importe quel moment.

CONSENTEMENT DU TUTEUR LÉGAL

(Pour les patients de moins de 16 ans)

Nom du tuteur légal: _____ Lien de parenté: _____

Signature du tuteur légal: _____ Date: _____

Témoin: _____ Date: _____

Chercheur: _____ Date: _____

ASSENTIMENT ÉCLAIRÉ

(À signer par les patients de moins de 16 ans)

Je, sous-signé(e), _____, comprends ce qui est exigé dans le cadre du projet et accepte d'y participer.

Signature du patient: _____

Date: _____



FORMULAIRE DE CONSENTEMENT

Nom du patient: _____ Date de naissance: _____

Nom du projet: **Les effets cliniques et attentionnels du traitement aigu à la nicotine dans le traitement du syndrome de Tourette**

J'ai lu et compris le texte du consentement éclairé à cette étude, et on a répondu à toutes mes questions. Je consens volontairement à ce que mon enfant participe à ce projet de recherche et je comprends que je peux l'en retirer à n'importe quel moment.

CONSENTEMENT DU TUTEUR LÉGAL

Nom du tuteur légal: _____ Lien de parenté: _____

Signature du tuteur légal: _____ Date: _____

Témoin: _____ Date: _____

Chercheur: _____ Date: _____

ASSENTIMENT ÉCLAIRÉ

Je, sous-signé(e), _____,
comprends ce qui est exigé dans le cadre du projet et accepte d'y participer.

Signature du patient: _____

Date: _____