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# Response of motor and cognitive speed to increasing doses of methylphenidate in children diagnosed with Attention Deficit /Hyperactivity Disorder

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## ABSTRACT

This study has examined the effect of 3 doses of Methylphenidate (MPH) on the speed of motor and cognitive performance in children diagnosed with ADHD. Thirty children clinically diagnosed with Attention Deficit /Hyperactivity Disorder (ADHD) aged 6-12 years were recruited through the ADHD Clinic and the Severe and Disruptive Behavior Disorders Program at the Douglas Mental Health University Institute. The three doses of MPH were administered according to a double blind randomized cross-over three day trial (0.3; 0.5 0.8 mg/kg/day in a bid schedule). An improvement across all three doses of MPH on motor, cognitive and behavioural measures was observed. The improvement is significant at low doses of MPH and an increase of dose up to 0.8 mg/kg/day does not lead to further improvement of the speed of simple motor task, but might be beneficial to specific cognitive tasks. No deterioration was observed in association with higher doses of MPH.

## RÉSUMÉ

Cette étude a examiné l'effet de trois doses de Méthylphénidate (MPH) sur la vitesse de la performance motrice et cognitive chez les enfants diagnostiqués avec le TDAH. Trente enfants avec un diagnostic clinique de trouble de déficit de l'attention/hyperactivité (TDAH), âgés entre 6 et 12 ans ont été recrutés par la Clinique TDAH et par le Programme des troubles disruptifs sévères du comportement de l'Institut Universitaire en Santé Mentale Douglas. Lors d'un essai thérapeutique à double insu qui s'échelonna sur trois jours, une dose différente de MPH (0.3; 0.5 et 0.8 mg/kg/jour sur un horaire bid) a été administrée aux enfants. Une amélioration de la performance a été observée à l'aide de mesure motrice, cognitive et comportementale sur chacune de ces trois doses de MPH. L'amélioration est significative à des faibles doses (0.3 mg/kg/jour) de MPH. Il n'y a pas d'augmentation significative de la vitesse lors des tâches motrices simples avec une dose plus élevée (0.8 mg/kg/jour), mais cette dose peut être bénéfique à des tâches cognitives spécifiques. Aucune détérioration n'a été observée en association avec des doses plus élevées de MPH.

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# INTRODUCTION

## *1. Rationale*

Attention Deficit/Hyperactivity Disorder (ADHD) is the most commonly diagnosed child psychopathology in North America, affecting 5-12% of school-aged children (Faraone et al., 2003) and worldwide (Polanczyk et al., 2007). It is characterized by developmentally inappropriate symptoms of inattention, impulsivity and motor restlessness (Diagnostic and Statistical Manual of Mental disorders - IV, 1994; Lahey et al., 1994). In addition to the clinical syndrome, it is now well established that subjects diagnosed with ADHD have more complex deficits affecting cognitive abilities (Nigg et al., 2002), academic performances (Barkley, 1997; Kempton et al., 1999) and motor coordination (Fliers et al., 2007; Klimkeit et al., 2005). Children with ADHD have also been reported to have specific emotional reactivity (Nigg, 2006).

For over 60 years, stimulant medications have been used in the treatment of ADHD. Methylphenidate (MPH) is the most frequently prescribed stimulant, thought to act at least partially by increasing synaptic levels of dopamine. More specifically, MPH has been shown to block the dopamine transporter, therefore increasing the synaptic level of dopamine (Biederman, 2005; Volkow et al., 2002). Therapeutic effects of MPH appear to be dose dependant (Arnsten & Dudley, 2005; Sprague & Sleator, 1977; Volkow et al., 2002). Most studies indicate that, within the tolerable dose, therapeutic effects of MPH are more or less linear, indicating that behaviors, as assessed by parents and teachers, improve with the increase of the dose of MPH (Barkley, 1991, Sprague, 1977). However, the dose-response curve of cognitive response is less clear. Several studies indicate that

the effect of MPH on cognitive performance follow an inverted "U" shape curve, whereby low-medium doses of MPH are associated with improved performances while higher doses are associated with deterioration (Arnsten & Dudley, 2005; Douglas et al., 1995; Sprague & Sleator, 1977). Other studies suggest a linear improvement with the increased doses of MPH (Pearson et al., 2004) and finally, some authors reported no changes in cognitive performances under MPH treatment (Tannock et al., 1989; Winsberg et al., 1982). These discrepancies may be due, at least in part, to the fact that different tasks have different

dose-response curves to methylphenidate (Berman et al., 1999; Rapport et. al., 1985). Indeed, different tasks may involve different brain regions with varying dopamine innervations and responses to treatment. For example, it has been shown that stimulant medications decrease dopamine levels in striatal area and increase dopamine in the frontal area of the brain (Díaz-Heijtz et al., 2006; Volkow, 2002)Thus, it is possible that the effects of MPH on different neuropsychological and motor output follow different dose-response curves, depending on the brain regions controlling the behavioural task under investigation. Determination of the optimal dose aiming at a particular function is an important clinical and research question. In this work, we tested the response of clinically significant behaviours and cognitive functions relevant for ADHD to three different doses of methylphenidate. In addition, under the same paradigms, we tested the response of fine motor behaviours to increasing does of methylphenidate. To our knowledge, there are only a few studies that examined the effect of stimulant treatment on fine motor functioning in children diagnosed with ADHD (Harvey et al., 2007; Klimkeit, Mattingley,

Sheppard, Lee, & Bradshaw, 2005) and no studies investigating the dose response of motor performance to methylphenidate.

# CHAPTER I: LITERATURE REVIEW

## *1.1 ADHD – An introduction*

The history of ADHD as a childhood psychopathology dates back to 1902, when a similar disorder was described by Still (Spencer, 2007; Spencer, 2007, Mick E., 2007). It was referred to as "minimal brain dysfunction" till the 1950s, when it was included in *Diagnostic and Statistical Manual of Mental Disorder* as "hyperactive child syndrome". Only with the release of *DSM-III* in 1980 was the emphasis put on the inattention as a significant part of the disorder.

The present diagnostic manual, *DSM-IV* differentiates three subtypes of ADHD: predominantly inattentive, predominantly hyperactive-impulsive, and combined subtype. At least 6 out of 9 symptoms of inattention or hyperactivity/impulsivity are required to make the diagnostic of the inattentive subtype or the hyperactive subtypes respectively. To diagnose the combined subtype, at least 6 symptoms of inattention and 6 symptoms of hyperactivity/impulsivity need to be present. Studies report that about 50- 60% of all individuals diagnosed with ADHD fall into the combined category, around 30% qualify as the inattentive type, and only 10-15 % are purely hyperactive (Millstein et al., 1997).

Studies report that, besides inattention and hyperactivity symptoms, children diagnosed with ADHD also have more complex impairments that affect their behaviour and social skills (Merrell & Wolfe, 1998). Furthermore, children diagnosed with ADHD

are more likely to have problematic relationships with their parents (Alessandri, 1992; DuPaul et al., 2001; Whalen & Henker, 1986) and peers (Greene & Ablon, 2001).

ADHD is more commonly diagnosed in boys, with a male to female ratio ranging from 10:1 in clinically referred samples to 3:1 in a community samples (Biederman et al., 2002). The gender difference in a clinical population seems to be at least partially due to the differences in phenotypic expression, such as higher levels of disruptive behaviour in boys resulting in referral bias (Stefanatos & Baron, 2007; Willcutt & Pennington, 2000). However, most studies suggest that there is no evidence of gender -specific characteristics within the clinically diagnosed samples in terms of clinical subtypes, social and cognitive profiles (Biederman et al., 2005, Seidman, 2005, Yang, 2004).

### *1.2 Cognitive and motor dysfunction in ADHD*

Over the last three decades, research of cognitive characteristics of children diagnosed with ADHD has led to the observation that there are a number of subtle, subclinical deficits commonly associated with ADHD. A meta-analytic review of 18 studies examining tests of executive function in children with ADHD suggests impairments in motor inhibition, working memory, vigilance, and perceptual speed (Pennington & Ozonoff, 1996). Another meta-analysis of 83 studies has shown that children with ADHD demonstrate significant impairment on measures of working memory, planning and organization, set shifting and processing speed (Willcutt, 2005). Other cognitive deficits associated with ADHD include slower speed of color naming (Banaschewski et al., 2006; Bedard, Ickowicz, & Tannock, 2002; Tannock, et al., 2000) and difficulties in some aspects of listening comprehension (McInnes, et al., 2007).

One of the most studied components of executive functions is working memory. An overview of twenty- six studies on working memory in ADHD population (Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005) suggests that working memory is deficient in ADHD, most consistently observed in measures of spatial memory. Nevertheless, some studies indicate that children with ADHD do not differ from controls on memory storage capacity (Benezra & Douglas, 1988).

Despite the anecdotal belief that hyperactive children have better movement abilities than their non-hyperactive healthy peers, recent studies suggest that there might be specific motor deficits associated with ADHD. It has been reported that ADHD is characterized by impaired motor abilities, such as motor coordination (Fliers et al., 2007; Harvey & Reid, 1997), motor planning (O'Driscoll et al., 2005; Poeta & Rosa-Neto, 2007) and motor control (Rommelse, 2007). Children with ADHD have slower and more variable arm movement (Yan & Thomas, 2002), slower reaction and movement times compared to controls (Klimkeit et al. ; Pedersen & Surburg, 2005). Furthermore, there have been indications of developmental delays in functions controlled by the vestibular system (Zhang, Yu, & Wang, 2007).

However, some studies fail to find differences between the ADHD and control groups on motor tasks when children diagnosed with coordination disorder are excluded from the analysis (T. M. Pitcher, Piek, & Hay, 2003). Studies fail to find differences between the ADHD population and control in the execution of timed movement (Klimkeit, Mattingley, Sheppard, Lee, & Bradshaw, 2005). Yet, for the subgroup of children diagnosed with ADHD and development coordination disorder, studies

consistently report significantly inferior performance on motor task compared to the age and sex matched controls.

Overall, studies of motor abilities in children diagnosed with ADHD provide some evidence that there is an impairment of motor functions; however, the results are inconsistent. While some researchers suggest that motor difficulties can be explained by attention deficit, others advocate that motor dysfunction cannot be explained by attention impairment and constitutes a separate impairment (T. M. Pitcher, Piek, & Hay, 2003).

Further investigation of the characteristics of cognitive and motor functioning is needed in order to determine whether the observed difficulties are the result of poor attention or specific impairments of cognitive and motor functions associated with ADHD.

### *1.3 Neuropsychological Models of ADHD*

Since the introduction of the diagnosis of ADHD as a disorder, few models have been suggested in the attempt to describe the core mechanism(s) of the deficits associated with ADHD.

The most widely accepted model of ADHD suggests that the core deficit underlying the clinical symptoms is a deficit in "response inhibition", also referred to as "inhibitory control" (R. A. Barkley, 1997). Response inhibition is the capacity of the individual to withhold a pre-potent response when engaged in a task. According to the model proposed by Barkley, this core deficit then leads to secondary impairments (R. A. Barkley, 1997). These secondary impairments lead to decreased control of motor behavior and poor sustained attention, which appear as clinical symptoms of ADHD: inattention, hyperactivity and impulsivity. Several studies have provided evidence that

children with ADHD indeed show deficits of inhibitory control (Logan, Cowan, & Davis, 1984; Nigg, 2001; Overtoom et al., 2002). According to this theory, behavioral inhibition directly influences the motor system and sets the incident for the executive function, which, in turn, directly affects the motor control (Barkley, 1997).

While Barkley's model suggests that the core deficit is mostly in top-down regulation of the executive functions, Sergeant's cognitive-energetic model (CEM) proposes that there are both top-down and down-top dysregulations associated with ADHD (Sergeant, 2005). The cognitive-energetic model implements three levels: the upper level is the executive control system, the middle level is the energetic pools: arousal, effort, and activation; and the lower level is the encoding stage, central for memory and motor function. These three levels are interactive with both a top-down and a bottom-up stream. It is suggested that the dysregulations of energetic level can explain deficit in executive functions associated with ADHD (Sergeant, 2005).

A more recent model has suggested that ADHD symptomatology might result from delay aversion, a tendency to select a smaller immediate reward versus a larger delayed reward. This emotional deregulation is believed to play a significant role in ADHD symptomatology. It is suggested that delay aversion is not correlated with the impairment of inhibitory control, and thus constitutes a separate pathway to ADHD populations. This model, proposed by Sonuga-Barke (Sonuga-Barke, 2002), suggests that there are two distinct pathways to ADHD. The first pathway posits that behavioral symptoms are resulting from poor inhibitory control and dysregulation of action. The second pathway posits an altered reward gradient over time whereby children have an aversion to reward delay. According to this dual-pathway model, these two subtypes are

characterized by different levels of symptoms, cognitive and motivation profiles, and have different genetic and non-genetic origins (Sonuga-Barke, 2002).

Though different in their definitions of core deficits underlying ADHD symptomatology, all these theories stress the importance of the executive function deficit in ADHD population. As further discussed, all these models have proposed that ADHD symptomatology results from certain neurobiological dysfunctions. The present line of neuroscience research attempts to determine the core neurobiological mechanisms responsible for the development of the disorder.

### *1.4. Neurobiological mechanisms of ADHD*

Although the aetiology of ADHD remains unclear, there is strong evidence that genetic factors are significant contributors to the development of this disorder, being responsible for as much as 80% of the ADHD symptoms (Faraone et al., 2005). Environmental factors such as maternal stress and complications during pregnancy, low birth weight, and stressful life events have also been shown to contribute to the development of the disorder (Grizenko,et al., 2008, Sasaluxnanon, 2005 ; Lee, Chang, & Lung, 2006). Though the mechanisms of interaction of genetic and environmental factors are still being investigated, it has been suggested that both environmental and genetic factors act through a dysregulating in dopaminergic brain systems (DiMaio, Grizenko, & Joober, 2003).

Early investigations of neurobiological mechanisms of ADHD noted similarities of ADHD symptoms with symptoms of brain injuries, specifically damages in the frontal and striatal areas (Bush, Valera, & Seidman, 2005; Diamond, 2005). It has been noted that the motor restlessness observed in ADHD patients is similar to the clinical syndrome

manifested by damage in the striatum. The impulsivity observed in ADHD is also reminiscent of the impulsivity observed in individuals with injured prefrontal cortex. Since striatum has close links with a prefrontal cortex, the fronto-striatal complex is considered central to the pathogenesis of ADHD.

These theoretical assumptions and clinical observations led to an increasing interest in brain imaging studies. There has been considerable progress over the last few years in determination of the possibly altered brain regions in ADHD using structural imaging, Position Emission Tomography (PET), Single Photon Emission Computed Tomography (SPECT) and, more recently, Functional Magnetic Resonance Imaging (fMRI) techniques.

It has been reported that there is a higher frontal and lower striatal activation during go-no-go task (Vaidya et al., 1998), hypoactivation of dorsal singular cortex (Bush et al., 1999) and a lower striatal activity while performing response-inhibition task [overview by (Bradley, 1937)] in children and adults diagnosed with ADHD compared to control groups.

A recent meta-analysis of neuroimaging studies of ADHD suggests that the largest differences between subjects diagnosed with ADHD and healthy controls include differences in cerebellar regions, the splenium of the corpus callosum, total and right cerebral volume, and the right caudate (Valera, Faraone, Murray, & Seidman, 2007). These findings support the theoretical assumption that there are specific motor coordination deficits associated with ADHD, since the cerebellum (Tseng, Diedrichsen, Krakauer, Shadmehr, & Bastian, 2007) and corpus callosum (Jea et al., 2008) are known to be responsible for motor coordination.

It has been reported that there is a higher frontal and lower striatal activation during go-no-go task compare to healthy controls (Vaidya et al., 1998). Lower striatal activity has been found in children and adults diagnosed with ADHD compared to controls when measures are taken during response-inhibition tasks. (Bush et al., 1999). These important findings suggest that difficulties that children and adults with ADHD experience on tasks requiring inhibition and interference control might be related to the dysfunction of the striatal area.

Though studies are inconsistent in the reporting of the implicated brain regions, overall most studies suggest that there is a dysregulation of dopamine neurotransmission in frontal-striatal circuitry. The results of functional imaging might be inconsistent due to the differences in tasks used while performing the imaging. However, these inconsistencies might indicate that the dysfunction of certain brain regions is only apparent while performing a specific task involving that region. Further support of the implication of dopamenergic system in the biology of the disorder can be found in the fact that pharmacological agents that act on the dopaminergic system are known to be effective in alleviating ADHD symptomatology.

### *1.5. Pharmacological treatment of ADHD*

Stimulants, including methylphenidate (MPH), are considered to be the treatment of choice for ADHD (Wigal et al., 1999). Since 1937, when stimulants were discovered to be effective in the treatment of hyperactivity symptoms by (Bradley, 1937), a vast amount of research has been done in the attempt to understand the effects of these pharmacological agents. It is estimated that about 3% of school aged children are treated with stimulants (Zito et al., 2003) that improve the core behavioural symptoms in

approximately 75 % of children (Greenhill et al., 2001; Solanto, 2002; Spencer et al., 1996). MPH peak concentration is observed within 60-90 minutes after the administration and its clinical effects are observed within 45 minutes (Volkow, Fowler, Wang, Ding, & Gatley, 2002). Although the exact mechanism responsible for the therapeutic effects of MPH is not clear, it has been established that MPH blocks the dopamine transporter and therefore blocks dopamine reuptake (Seeman & Madras, 1998). Recent studies using the PET and MRI suggest that MPH-induced increase of extra-cellular dopamine improves attention and decreases distractibility. It has been suggested that since dopamine modulates motivation, the increases in dopamine might facilitate the interest elicited by tasks and, therefore, improve performances (Volkow, Fowler, Wang, Ding, & Gatley, 2002).

Therapeutic response to MPH is characterized by reduction of motor hyperactivity, improved attention, and increased impulse-control *(Diagnostic and Statistical Manual of Mental Disorders - IV*, 1994). Stimulants have been shown to have beneficial effects on observable behaviour in classrooms (Bennett, 1999), on impulse control, and on decreasing reaction time on both simple and complex tasks (Reid & Borkowski, 1984). The effects of MPH have short-term as well as long-term effects (Hechtman, 2006; Jensen, 2002), and the Multimodal Treatment studies of ADHD suggest that the most effective treatment of ADHD is pharmacological treatment with MPH combined with behavioural therapy (Vitiello et al., 2001; Shaywitz, Fletcher, & Shaywitz, 2001).

While most studies are consistent in reporting behavioural improvement associated with MPH treatment, the effects on cognitive performance are less clear.

Tannock et al. (Tannock & Schachar, 1992), suggested that MPH has negative effect for cognitive flexibility while other authors indicate that MPH improves persistency without impairing flexibility (Douglas, Barr, Desilets, & Sherman, 1995); (Pelham, Hoza, Kipp, Gnagy, & Trane, 1997). On the contrary, Lufi et al. (Lufi, Parish-Plass, & Gai, 1997) did not observe changes in cognitive characteristics with the MPH treatment, a result partially confirmed by Coghill et al., who reported no change in the performance on spatial tasks, and no effect on the accuracy on go-no-go tasks under MPH (Coghill, Rhodes, & Matthews, 2007).

Some authors suggest that the effects of MPH could be task dependant. MPH might decrease the speed of the cognitive performance only on the complex tasks (Berman, Douglas, & Barr, 1999). However, this slowness associated with MPH might be compensatory and could be a sign of better self-regulation that leads to improved adaptation to the characteristics of the task (Berman, Douglas, & Barr, 1999). Furthermore, some studies report larger improvement under MPH in people whose performance is more impaired while off medication (Boonstra, Kooij, Oosterlaan, Sergeant & Buitelaar, 2005).

The studies analyzing the effects of MPH on motor performance provide inconsistent results. As previously discussed in *chapter 1.2*, it is still unclear whether there is a specific motor function impairment associated with ADHD, and if this impairment is improved under the treatment with MPH. For example, Klimkeit (Klimkeit, Mattingley, Sheppard, Lee, & Bradshaw, 2005) reports that children with ADHD show significantly slower reaction time (Harvey et al., 2006), and this difference tends to disappear with MPH. However, Harvey et al., (Harvey et al., 2007) did not find any effect

of MPH on motor skills in a placebo-controlled study. Overall, it seems that motor response becomes faster with medication, yet treatment has no effect on the accuracy of movements (Pedersen & Surburg, 2005).

The studies of the effects of MPH on cognitive performance are inconsistent in their findings partially due to the variability of the measures used across the studies. Moreover, different studies are based on different doses of MPH. Furthermore, MPH can be made in different formulations, regular or slow release, that might have at least minor variation in their affects due to the differences in pharmacokinetic (more rapid absorption and higher peak in plasma level is observed for regular MPH) and pharmacodynamics (longer effects for Slow Release) of these formulations (Markowitz, 2003, Markowitz J. et al. 2003).

### *1.6 Dose dependent effects of MPH*

Most researchers underline high individual variability in response to stimulant medication and stress the importance of titrating the dose in each patient. The range of dose-response is very wide, with some children responding to as little as 0.1 mg/kg and exceptional cases where response was observed only at very high doses [6.1 mg/kg (Lipkin, Butz, & Cozen, 2003)]. Generally, low doses range between 0.3 to 0.5 mg/kg, medium doses between 0.5 and 0.7 mg/kg and high doses are between 0.5 and 1.0 mg/Kg. The sources of this variability are not well understood and may depend on various factors. It is possible that response to methylphenidate may depend on genetic factors. Indeed, it has been reported that therapeutic response, that is response evaluated according to clinical outcome, is correlated in siblings (Van der Meulen, E. M., S. C. Bakker, et al., 2005). More recently, we have shown in our laboratory that the gene coding for the dopamine transporter, the main mechanism of clearing dopamine from the synapse,

modulates therapeutic response to methylphenidate as assessed by parents but not by teachers (Joober and Sengupta, 2006). This indicates that response to methylphenidate may be a complex phenotype and that different behavioural and cognitive traits relevant for ADHD may present different profiles of response to methylphenidate. In fact, while most studies consistently indicate that the optimal behavioural improvement is observed on 0.8-1.0 mg/kg/day dose of MPH (Sprague & Sleator, 1977), it has been suggested that the dose of the optimal cognitive response to MPH may be observed at lower doses (0.3 mg/kg) in children with ADHD. In one of the earliest studies examining this question, a linear improvement of most cognitive functions was observed with increasing doses of MPH up to 0.6 mg/kg/day (Benezra & Douglas, 1988). Other studies also have indicated that most of the cognitive benefits occur at a low to medium dose (0.3-0.6mg/kg/day) of MPH and that higher doses are associated with deteriorating effects, inducing perseverative behaviour (Tannock, 1995, 1995), and increasing reaction time (Berman, Douglas, & Barr, 1999). For ecological measures of cognitive performance at school, low doses (0.2-0.4 mg/kg/day) of MPH have been shown to be the most beneficial, whereas higher dose of MPH seem to have negative effect on academic performance in school measured outcomes. (Evans et al., 2001) Overall, these studies suggest that while dose-response functions for clinically relevant behaviours were linear, response on tasks measuring cognitive functions level off or even deteriorate with an increasing dose.

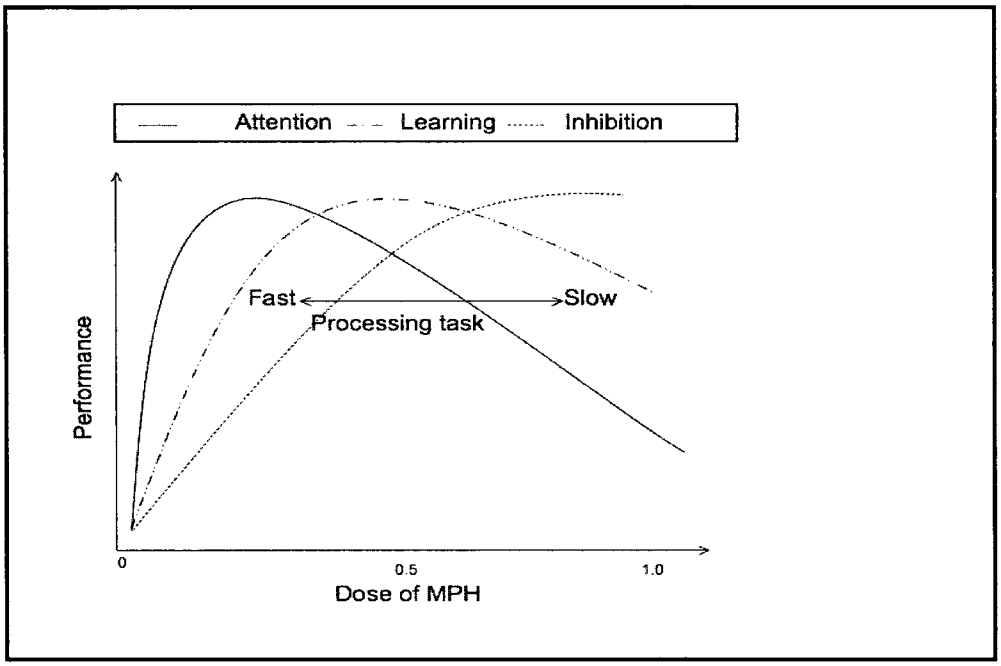
In contrast, Barkley reported that, within clinically tolerable doses (5 and 15 mg bid), beneficial effects of MPH on cognitive performances do not change with higher doses of MPH (Barkley, DuPaul, & McMurray, 1991). Few other studies suggested linear improvement of cognitive function associated with the increase of dose of MPH. Higher

doses seem to be more beneficial for the complex tasks (O'Toole, Abramowitz, Morris, & Dulcan, 1997) and for the tasks requiring inhibitory control (Stein et al., 2003).

The dose-response curves of motor behavior have not been well investigated, although some studies suggest certain slowness and increase in reaction time associated with the higher doses of MPH. Thus, further investigation of dose effects of MPH on the speed of motor performance is needed.

In a review of 81 studies investigating dose-response curves to MPH, Rapport and Kelly identified equal numbers of studies reporting and not reporting differences between low and high doses of MPH (38.5%). The rest of the reviewed studies (25%) had inconclusive results. The authors of this review emphasized the importance of further investigating dose-response curves to MPH on cognitive functions, since only 13 of these studies contrasted low versus high dose conditions (Rapport & Kelly, 1991). Based on the analysis of a subsample of 16 studies, Rapport and Kelly suggested that automatic and less effortful processing has an optimal response on low doses of MPH (0.2-0.4 mg/kg day), levels off at medium doses and then deteriorates at higher doses. In contrast, tasks that require slow processing and increased effort, like behavioral inhibition, organization, and strategic planning may show a more linear dose response curve with optimal improvements at higher doses of MPH (0.7 – 0.9 mg/kg). As shown in Figure 1, behaviors with intermediate complexity may show intermediate dose response curves (Rapport & Kelly 1991).

Figure 1: (Rapport & Kelly, 1991).




In the suggested model, Rapport and Kelly further imply that differences found in the dose-response curves on various cognitive processes can be most probably explained by the involvement of different, yet interdependent, biological systems in the pathogenesis of ADHD.

In conclusion, dose-response studies of MPH indicate that, within the tolerable range, there is a linear improvement with higher doses of MPH. However, the effects of MPH on cognitive and motor performance need further investigation. A number of variables may explain the various and sometimes divergent results reported by the different studies. From this review of the literature, it appears that the nature and the complexity of the task under investigation may be, at least in part, a source of variability between studies. Indeed, two different tasks involving different or partially overlapping brain regions in their processing may show different dose response curves to methylphenidate. This is because dopamine, the main target of treatment with methylphenidate, may be differentially responding to treatment with methylphenidate in

different brain regions. It is possible for example, that stratium, a brain region that is very rich in the dopamine transporter (blocked by methylphenidate), may be subject to a higher increase of dopamine during treatment with methylphenidate as compared to the prefrontal cortex, a region considered poor in dopamine transporter.

Another important parameter that seems to be implicated in the dose response curves to methylphenidate is the complexity of the task. Tasks that are complex may require coordination in different brain regions, and therefore their response to methylphenidate may show a complex dynamic.

In this study, we selected tasks (Stroop *vs.* Purdue Pegboard Test) that are probably partially different with respect to the main locus of their neurocognitive processing (prefrontal *vs.* striatum), which have varying degrees of complexities to test the dose-response curves to methylphenidate.

These tasks are also contrasted by the fact that the behavioural output in the former is entirely verbal, whereas the latter is an entirely motor task.

In addition, we selected a task that is more in line with the daily activities of the child and that is often impaired in children with ADHD: the restricted academic situation scale (see below for description of the task).

### *Hypotheses and aims:*

The speed of the performance of the Stroop and the Purdue Pegboard are correlated. The correlation is more likely to be stronger for simple parts of the tasks, requiring automatic response, rather than for more complex subtests.

This will be tested in a sample of 77 children who have been tested with both the Stroop and the Perdue Pegboard tests while they are not taking any medication for at least 7 days.

Dose-response curves to methylphenidate will show left shifted inverted-U shaped curves for simpler tasks and right shifted inverted-U shaped curves for more complex tasks.

# CHAPTER II: METHOD

## *2.1 Design of the study:*

The present study has a double-blind randomized cross -over design. The participants completed a three day medication trial, where tests were conducted prior to the administration of treatment and 60 minutes after the administration of treatment. We chose to test 60 minutes after the administration of treatment because MPH has been shown to have effects within the 45 minutes time frame (Volkow, Fowler, Wang, Ding, & Gatley, 2002).

The treatment is delivered in the forms of identical gelatine capsules prepared by the study pharmacist and put in the individual packages for each day according to the participants' weight (0.3 mg/kg/day; 0.5 mg/kg/day; 0.8 mg/kg/day) in a twice daily dose. Some studies have used fixed doses for all participants (Pelham et al., 2001; Rapport, Quinn, DuPaul, Quinn, & Kelly, 1989). However, titrating with individualized per kilogram of body weight dosing allows more precise evaluation of the dose effect. In the present study we used the fast release MPH, as it is harder to titrate with per kilogram dose with other formulations. In addition, slow release formulations might add another layer of variability as subjects may have important pharmacokinetic differences. Methylphenidate is a short-acting stimulant with a duration of action of 4 hours on average, with a short pharmacokinetic half-life of 2-3 hours (Kimko, Cross, & Abernethy, 1999). Since MPH is characterized by short release and short time of action, we have been able to perform testing before and 60 min after the administration of the treatment within the same day, and be less concerned about the build-up of medication described as the "carry-over" effect form one day to the next. Due to technicalities of the dose

preparations, the dose precision was possible only up to 1.25 mg., with the smallest dose being 5 mg. A table with weight-dose correspondence was created and dose preparation was done according to this table (see Appendix 1).

For the randomization of the treatment conditions, a Latin Square procedure was followed (30 subjects and 3 treatment conditions ( Table 1).

**Table 1:** The randomization of subjects across three doses of MPH

| Day 1 | Day2 | Day3 |
|---|---|---|
| Low (N=10) | Medium (N=10) | High (10) |
| Medium (N=10) | High (N=10) | Low (N=10) |
| High (N=10) | Low (N=10) | Medium (N=10) |

### *2.2. Participants:*

Seventy-one children between 6 and 12 years of age diagnosed with ADHD by a psychiatrist were recruited through the ADHD clinic and the Severe and Disruptive Behaviour Disorders Program at the Douglas Mental Health University Institute. We restricted the age to the 6-12 range because ADHD is usually not diagnosed before the age of six, and because, by the age of 13, some children start puberty; hence, they undergo important cognitive changes. In addition, the response to medication in preschoolers and adolescents has been reported to differ from school aged children. Prior to the three day titration study, children completed a baseline assessment while off medication for at least 7 days. The assessment included a measure of motor performances (Purdue Pegboard Test) and a measure of speed of verbal naming (STROOP Color and Word Test).

All children completed a Wechsler Intelligence Test for Children (Abikoff, 2001; Barkley, 2004) to evaluate their IQ. Children with the full scale IQ below 70, Tourette Syndrome, pervasive developmental disorder, psychosis or any medical condition or impairment that may interfere with the child's ability to complete the study were excluded.

The study has been approved by the Ethics Research Board of the Douglas Hospital (Appendix 2). The written parental consent and child verbal assent has been obtained for all participants (Appendix 3).

Thirty-three children accepted to be enrolled in a three day double-blind cross-over titration study. Each child in this subgroup received three doses of MPH (0.3, 0.5; 0.8 mg/kg/day) on three consecutive days. In order to keep the conditions as constant as possible over the three testing days, the same research assistant conducted all the testing during the three experimental days. All the testing was conducted in the morning at the same time between 9 and 10 a.m. The tests were conducted both prior to and 60 minutes after the administration of the treatment. During the testing day, the child was brought to the clinic and the testing was started before the administration of the treatment. The tests were administered in the following order: Purdue Pegboard, STROOP Color and Word Test, then Restricted Academic Setting Scale. After the testing was finished, the treatment was administered and the child was allowed a free time of 60 minutes. Immediately after this period, the testing session was resumed and the tests were administered in the same order.

### *2.3 Assessment tools*

Since many children with ADHD were shown to perform worse and with higher variability on longer tasks (Barkley, McMurray, Edelbrock, & Robbins, 1990), tasks with a short time of administration were selected. Both STROOP and Purdue Pegboard Tests have short administration time (about 3 minutes each). Short time of administration also minimized the influence of attention dysfunction on the measure of motor and verbal performance. It could also decrease day-to-day variability. Stoop Color and Word and the Perdue Pegboard tests have been shown to have minimal practice effect (Bedard, Ickowicz, & Tannock, 2002; *Purdue Pegboard Quick Reference Guide*, 1999), and randomized order of the doses allowed control for the possible practice effect.

**Perdue Pegboard test:**

The Purdue Pegboard Test (Tiffin & Asher, 1948) was originally designed for the personnel selection for manual work, but has been suggested as a neuropsychological assessment tool by several authors (T. M. Pitcher, Piek, & Hay, 2003). The test has normative data based on a sample of 1334 school-aged normal children. To our knowledge, only one study has examined the performance of ADHD children on the Purdue Pegboard task (*Purdue Pegboard Quick Reference Guide*, 1999) and no studies have investigated the dose-effect of methylphenidate on this test's performances. Purdue Pegboard Task consists of four parts. For the first part, children were asked to insert pins in the holes as fast as they can, taking one pin at a time using their *dominant hand* from the corresponding cup built in the board (see Appendix 4). Children were given time to practice to assure that they understand the instructions. For the second part, children were asked to perform exactly the same tasks with the *non-dominant* hand. For the third part,

they were instructed to take pins with two hands simultaneously. The number of pins inserted within 30 seconds interval was calculated for each of these three parts. In the last part, or the *assembly part*, children were asked to first place a pin with their dominant hand, then a washer on the pin with the non-dominant hand, then a collar on top of the washer with a dominant hand, and finally another washer with the non-dominant hand. Children were asked to proceed as fast as they could for 60 seconds, and the number of inserted items was calculated at the end of this time period.

This test offers a graded increase of the complexity of the task with higher involvement of the prefrontal cortex in the last two parts, as it involves more planning and behavioural control compared to the simpler and quasi-automatic task of placing pegs in the holes of the board.

**Stroop Color and Word Test**

The Stroop Color and Word Task (Stroop) test (Golden, 2003) has been widely used in different populations and was standardized for children. In the first part of the test, the child is presented with a letter size page with 100 words that signify three colors (red, green and blue) printed in black ink and is asked to read them out loud as fast as possible within 45 seconds. In the second part, the child is presented with the same words printed with congruent colors and is asked to name the colors in which the words are printed as fast as possible within the 45 seconds interval. These two parts require simple reading skills and color recognition without interference. In the third part, the child is presented with the page of the same words printed with incongruent colors and asked to name the colors of the words. This part of the task requires both simple abilities needed in the previous two parts (reading and color recognition), but heavily involves inhibition control

that depends on the prefrontal cortex integrity. The **Stroop effect** is a demonstration of interference in the reaction time of this task. When a word such as "blue," "green," "red," etc. is printed in a color differing from the color expressed by the word's semantic meaning (e.g. the word "red" printed in blue ink), a delay occurs in the processing of the word's color, leading to slower test reaction times and an increase in mistakes. The effect is named after John Ridley Stroop who first published the effect in English in 1935.

**The Restricted Academic Situation Scale (RASS).**

The Restricted Academic Situation Scale (RASS) is a coding system designed to observe and record the behaviour of a child assigned a set of math problems (based on the child's current grade) during a simulated independent academic situation within a clinical setting (Krikorian, Bartok, & Gay, 1994). It is an assessment of the child's ability for sustained attention to routine, repetitive academic work in the presence of potential distractions, with no adult supervision. This scale has been used to discriminate between children with ADHD and normal controls as well as from those with conduct problems unrelated to ADHD.

The Restricted Academic Situation was set up in a clinic playroom containing toys, a work table, a chair and an intercom (Golden, 2003). After allowing the child to play for 5 minutes, used as a habituation period, the child was given a set of math problems with instructions to complete as many problems as possible, not to leave the seat, and not to play with any of the toys in the room. The child's behaviour was then assessed from behind a one-way mirror over a 15 minute time period. Behavioural events were recorded at 30-second intervals according to five categories: *off-task* (looking away from the task sheet), *playing with objects* (touching any object not directly used in the task),

*out of seat* (lifting buttocks off chair or moving chair), *vocalizing* (any vocal noise, whether task related or not), and *fidgeting* (repetitive, purposeless movements). The RASS score is the total number of recorded behavioural events in the 15-minute period. In a study completed by our laboratory (Karama et al., in press), which was completed using principal component analysis, followed by a confirmatory maximum likelihood factor analysis, it has been shown that the RASS is composed of two main factors: Task Disengagement (TD) and Motor Activation (MA). Task Disengagement is contributed by the scores obtained on *off-task, playing with objects* and *out of seat scales of the RASS,* and Motor Activation consisted of the *fidgeting* scale. Only TD was inversely correlated with age, indicating that TD and MA may be differentially modulated during development (Karama et al., in press). Furthermore, we have shown that only TD is modulated by the COMT Val/Met Genotype, which adds validity to the distinction between these two dimensions of this test (Sengupta et al., in press).

### *2.4. Statistical Analysis:*

To perform statistical analysis we used SPSS software. Continuous variables were expressed as means ± standard deviation (SD). Categorical variables were expressed as proportions (%). Chi Square analysis was used to compare proportions between groups.

Pearson correlation analysis was conducted in order to assess the relationship between speed of motor performance as measured by Purdue Pegboard and verbal performance as measured by Stroop Color and Word Task in children with ADHD. A one way ANOVA was performed in order to analyze the effect of clinical subtypes on the motor and verbal performance, where three clinical subtypes were considered as independent variables, and scores on Purdue Pegboard, Stroop Color and Word Tests

were considered as dependent variables. To account for the multiple comparisons of variables that might not be considered fully independent, we set a more conservative threshold of significance at 0.001.

A two-way, ,within subject (MPH dose and time) analysis of variance, in which MPH dose (0.3, 0.5, 0.8 mg/kg/day) and time (pre-medication and post-treatment) were the independent variables, and scores on behavioral and cognitive measures ( Purdue Pegboard, STROOP and RASS scores) were the dependent variables, was conducted using SPSS General Linear Model procedure (GLM).

To further examine the structure of cognitive measures, a principal component analysis was carried out for all subtests of Purdue Pegboard and Stroop Color and Word tests. Only principal components corresponding to eigevalues ≥1 were retained.

To study the structure of the behavioral measures used in Restricted Academic Situation Scale, a principal component analysis was carried out. Only principal components corresponding to eigevalues ≥1 were retained for analyses.

A one-way, within subject repeated measures analysis of variance, was performed in order to analyze the rate of improvement associated with each dose of MPH for each of the retained principal components. The improvement was calculated as the difference between the scores obtained before and those obtained 60 minutes after the administration of the treatment. The dose was considered the independent variable, and the change test was the dependant variable.

# CHAPTER III: RESULTS

## *3.1 Part 1: Baseline assessment*

### *3.1.1 Demographic characteristics*

Demographic characteristics of children who participated in the initial baseline assessment are represented in Table 2.

**Table 2:** Demographic characteristics of the sample that completed baseline evaluation.

| | N (%) |
|---|---|
| Gender ( males/ females ) | 55 (77.5%) / 16 (22.5%) |
| IQ (n=61): Mean ( SD) | 95.07 (11.5) |
| Ethnicity: white (%) /other (%) | 56 (79%) / 15(21%) |
| SES:< $20.000<br>$20.000-40.000<br>> $40.000 | 23 (32.4%)<br>13 (18.4 %)<br>33 (46.5%) |
| Age | Mean = 9.0 / SD = 1.58 |
| Handiness ( right/left handed)* | 61 / 10 |
| Ever on Medication for ADHD (yes /no ) | 21 /50 |
| Number of inattentive symptoms** | mean = 7.75 / SD = 1.58 |
| Number of hyperactivity symptoms* * | mean = 6.42 / SD= 2.48 |
| Subtype of ADHD ** | Inattentive 19 (26.8%)<br>Hyperactive 5 (7%)<br>Combined 47 (66.2%) |

* - Assessed at the baseline (based on the hand child writes with)

** - Based on DSM-IV checklist filled by a treating psychiatrist

The ratio of boys to girls is 3.5:1, which corresponds to the clinically-referred population across the world (Nigg, 2006).

There were no significant gender effects on any of the subtests of the Purdue Pegboard or the Stoop subtests (all t-test p>0.05).

There were no significant differences between the clinical subtypes of ADHD with regard to the performance on Stroop Color and Word Test and Purdue Pegboard Task as revealed by one-way ANOVA's analysis ( $p>0.05$).

*3.1.2. Characteristics of Motor Performance*

As opposed to the Stroop task, fine motor skills have not been very well studied in children with ADHD. Thus, we decided to include a relatively detailed description of the results of the Perdue Pegboard performances.

To examine the performance of children diagnosed with ADHD on motor task, the scores of children were obtained during the baseline evaluation after a wash-out period of at least one week. For each age group, the Scoring Manual of the Purdue Pegboard Task provides Means and Standard Deviations obtained for the healthy controls, yet no standardized scores are available. Our data indicates that there are over 15 % of children who fall under one standard deviation (SD) from the mean of the population on the dominant, non-dominant and simultaneous hands subtests of the Purdue Pegboard. Over 3% of children perform worse than two standard deviations below the age mean. There were no children in our sample who performed above two SD and no children performed above one SD with their dominant hand. The chi-square analysis suggests that this distribution is not significantly different from what is expected according to the normal distribution ($p>0,05$). The performance on the Assembly subtest of the Purdue Pegboard was characterized by higher variability and better performance than for other subtests, with 10% of children performing better than one SD over the mean.

Purdue Pegboard manual (Bedard, Ickowicz, & Tannock, 2002; *Purdue Pegboard Quick Reference Guide*, 1999) provides the percentile scores for each of the subtests.

*Table 3* shows the percentages of the data that falls outside the 10th and 90th percentiles. The Chi-square analysis was performed to see whether the distribution of low and high scores is different from normally distributed scores, with an assumption that 10 % of scores would fall under the 10th percentile and 10% of score would fall over the 90th percentile. There are significantly more children who perform under 10th percentile on the Dominant hand subtest of Purdue Pegboard.

**Table 3:** Purdue Pegboard Performance on Baseline

| | Below 10th percentile | Over 90th percentile | Chi-square |
|---|---|---|---|
| Dominant | n= 22 (30%) | n=1 (1.4%) | Chi = 34.71** |
| Non-dominant | n=14 (19.7%) | n=1 (1.4%) | Chi = 12.16** |
| Both hands | n=19 (26.8 %) | n= 2 (2.8 %) | Chi =25.0** |
| Assembly | n=8 (11.3 %) | n= 6 (8.5%) | Chi=0.28 |

*p<0.05 ;**p<0.01;

This analysis indicates that the scores of children diagnosed with ADHD are significantly below the norms for the scores obtained on Dominant, Non-Dominant and Both hands subtests, but not in the assembly subtest.

*3.1.3. Characteristics of Verbal Performance*

For the Stroop Word naming scale the mean of the performance was analyzed in a similar manner. The distribution of the t-scores is represented by Table 4. There are no children who performed under two SD of the expected mean ( t-score less than 30) and two children who performed over two SD of the normative scores ( t-score more than 70). For the Color Naming there is one child who performed over two SD, and no children who performed worse than two SD below the mean. For the Color-Word Scale and Interference Scales all children performed within two standard deviations from the mean.

**Table 4:** Stroop Performance on Baseline

| | Below 2 SD | Over 2 SD | Chi-square |
|---|---|---|---|
| Word | 0 | 2 (2.8%) | 1.04 ( p>0.05) |
| Color | 0 | 1(1.4%) | 1.12( p>0.05) |
| Color-Word | 4 (5.6 %) | 0 | 1.2 ( p>0.05) |
| Interference | 0 | 0 | 1.5 ( P>0.05) |

The Manual for Experimental and Clinical Uses for Color and Word test (Golden, 1978) provides t-scores for each raw score for all four scales of the STROOP. A one sample t – test was performed in order to assess whether the t-scores of ADHD children are significantly different from the normative data (Mean T score =50, SD=10) as represented by ***Table 5.***

**Table 5:** Mean T-scores for each scale of the Stroop Color and Word Test

| | Mean t-score | t ( Sig. (2-tailed) |
|---|---|---|
| Word T-Score (T-Score) | 51.38 (11.7) | t=0.99 (p= .325) |
| Color Naming T- Score | 47.4 (6.6) | t= 3.3 (p=.001) |
| Color-Word T- Score | 43.46 (9.8) | t =5,62(p<.001) |
| Interference T- Score | 50.85(7.5) | t=0.95 (p>0.05) |

The results of the one sample t-test suggest that there is no difference in the performance of children diagnosed with ADHD and performance expected in normally developing children on the Interference scale (p>0.05). However, our analysis suggests that children with ADHD obtain lower scores on the Color Naming scale (t=3.3 p<0.01) and on the Color-Word scale (p<0.001).

### *3.1.4 Association between measures*

In order to examine the association between different measures of neurocognitive functioning that require quick timed response, Pearson correlation analysis between scores obtained on Purdue Pegboard and Stroop Color was performed. The results of Pearson correlation analysis are represented by Table 6. To account for the number of comparisons that were implemented in our analysis the $p$ value significance threshold was set at 0.01 level.

Color and Word Tasks.

| | | Word[1] | Color[2] | C-W[3] | Interf[4] | PP Dom[5] | PP Non Dom[6] | PP Both[7] | PP Sum |
|---|---|---|---|---|---|---|---|---|---|
| Word[1] | | | | | | | | | |
| | | | | | | | | | |
| Color [2] | Pearson r | .71** | | | | | | | |
| | p | .000 | | | | | | | |
| C-W [3] | Pearson r | .24 | .54** | | | | | | |
| | p | .041 | .000 | | | | | | |
| Interf [4] | Pearson r | -.63** | -.71** | .20 | | | | | |
| | p | .000 | .000 | .100 | | | | | |
| PP Dom | Pearson r | .57** | .53** | .31** | -.37** | | | | |
| | p | .000 | .000 | .010 | .002 | | | | |
| PP Non-Dom[6] | Pearson r | .50** | .49** | .24 | -.34** | .65** | | | |
| | P | .000 | .000 | .04 | .001 | .000 | | | |
| PP Both[7] | Pearson r | .58** | .53** | .20 | -.47** | .62** | .59** | | |
| | p | .000 | .000 | .09 | .000 | .000 | .000 | | |
| PP Sum[9] | Pearson r | 0.64** | 0.58** | 0.23* | -0.49** | 0.87** | 0.85** | 0.87 | |
| | p | 0.000 | 0.000 | 0.02 | 0.01 | 0.00 | 0.00 | 0.00 | |
| PP Assem[8] | Pearson r | .58** | .59** | .49** | -.32** | .65** | .57** | .69** | 0.73** |
| | p | .000 | .000 | .000 | .007 | .000 | .000 | .000 | 0.00 |

[1] Stroop Word – number of correctly named words on the Word Subtest of Stroop Color and Word Test ; [2] Stroop Color – number of correctly named colors on the Color Subtest of Stroop Color and Word Test ;[3] Stroop C-W –number of correctly named colors on the Color-Word Subtest of Stroop Color and Word Test;[4] Stroop Interference – Score obtained for the Interference ;[5] PP Dom – Purdue

Pegboard Dominant Hand condition;[6] PP Non-Dom- Purdue Pegboard Non-Dominant Hand condition ;[7] PP Non-Both- Purdue Pegboard Both Hands

[8]PP Sum- A sum of Dominant, Non-Dominant and Both Hands scores;[9] PP Asem- Purdue Pegboard Assembly Score

Our analysis indicates that the scales of the STROOP are correlated between each other. There is a strong association between Word Naming and Color Naming scales ($r=0.71$, $p<0.0001$). There is a medium strength correlation between the Color-Word scale (incongruent colors and words) and Color scale ($r=0.54$, $P<0.000$). However, the correlation between the Color-Word and Word naming is weak ($r= 0.24$) and not significant at the $\alpha > 0.01$ level. The Interference scores do not correlate with the Color-Word scores ($p>0.05$), yet have a strong correlation with Word Naming ($r = 0.63$, $p< 0.001$) and Color naming ($r=0.71$ $p<0.001$).

Our analysis indicates that there is a strong association between the sub-scores of the Purdue Pegboard. The Dominant Hand scores are correlated with Non-Dominant ($r=0.65$), with Both Hands ($r = 0.59$), the Sum ($r =0.86$) and Assembly scores ($r= 0.65$), all at the $p<0.01$. The Non-Dominant hand scores are also correlated with Both Hand ($r=0.69$), Sum ($r = 0.84$) and Assembly scores ( $r>0.5$), all at $p<0.01$. Both Hands scores are correlated with the Sum score ($r= 0.87$) and Assembly ($r = 0.84$) at $p<0.01$. The Sum of scores is highly correlated with the Assembly score ($r>0.7$, $p<0.01$).

Furthermore, our analysis indicates that there is a correlation between the sub-scores of Purdue Pegboard and the scales of the Stroop.

There is a medium strength association ($r > 0.5$) between the scores obtained on the Dominant Hand Subtest of Purdue Pegboard and Word Naming Scale of the Stroop

Task. There is a highly significant medium strength association between all four subtests of the Purdue Pegboard ($r>0.5$; $p<0.001$).

There is also significant medium strength association between the scores obtained on the Dominant hand condition of Purdue Pegboard and Word Naming scores ( $r = 0.57$, $p<0.001$), and between the Dominant hand condition of Purdue Pegboard and Color Naming Subtest of the Stroop ($r=0.53$, $p< 0.001$).

A similar association was revealed for the scores on Non-Dominant subtest and Word Naming Scale ($r = 0.50$; $p< 0,001$). A slightly lower degree of association was found between the performances on the Non-dominant hand subtest of the Purdue Pegboard and Color Naming scale of the Stroop ( $r=0.49$ $p< 0.0001$).

There is a weaker degree of association between the Interference Scores of the Stroop with the scores on the Dominant hand ( $r = 0.367$, $p<0.01$), Non-Dominant hand ( $r=0.398$ $p=0.01$), Both hands ( $r=0.472$, $p< 0.000$) , Sum Score ($p=0.49$, *$p<0.01$*)and Assembly ( $r= 0.316$, $p< 0.001$).

To further explore the structure of the relationship between the measures, we carried out a Principal Component Analysis (PCA) which suggested a two factor loading as represented in ***Table 7***.

**Table 7:** Factor Analyses (PCA) for the STROOP and Purdue Pegboard Scales.

| | Motor-cognitive | Interference Control |
|---|---|---|
| Stroop Word Score | .82 | -.20 |
| Stroop Color Score | .85 | -.00 |
| Stroop Color-Word Score | .43 | .70 |
| Stroop Interference Score | -.64 | .79 |
| Purdue Pegboard Dominant Hand Score | .79 | .09 |
| Purdue Pegboard Non Dominant Hand Score | .75 | .01 |
| Purdue Pegboard Both Hands Score | .80 | -.07 |
| Purdue Pegboard Sum[1] | .97 | 0.01 |
| Purdue Pegboard Assembly Raw Score | .82 | .28 |
| Eigenvalues | 5.80 | 1.33 |

[1]Purdue Pegboard Sum - A sum of Dominant, Non-dominant and Both hands scores

The first factor, Motor-Cognitive, is almost equally loaded by Word Naming, Color Naming and all four of the Purdue Pegboard subtests. The second, Interference Factor, is loaded by the Interference Score and Color-Word Score of the Stroop. However, the Color and Word Score seem to be contributing to both factors. Furthermore, Pearson correlation analysis indicates that Word Color and Interference Score are not correlated ($p>0.05$). As presented in part 3.2.3 (see Table 6) of this section, while the loadings of the first factor persist over different medication conditions, the loadings of the second factor are less consistent.

In conclusion, the results of these analyses indicate that simple and automatic tasks, regardless of the behavioral output modalities (motor or verbal), are highly correlated and seem to represent one factor. However, the Stroop Interference Score stands out as a different dimension that is likely to be sustained by different neuropsychological, neuro-chemical and possibly brain regions.

### *3.2 Part 2: Titration*

*3.2.1 Demographic characteristics of the participants*

Out of the 71 children who participated in the baseline part of the study, 33 participated in the titration part of the project. Three subjects were excluded from the analysis: two subjects were not administered 0.8 mg/kg/day dose and were given a lower dose due to clinical reasons (high body weight, and/or previously reported side-effects), and one child was uncooperative during two out of the three days of the testing. Clinical and demographic characteristics of two groups of children, those who participated in the titration part of the study and those who participated only in the first part of our study, are represented by Table 5.

**Table 5:** Demographic and clinical characteristics of children participated in the titration and children who did not participate in titration study.

| Characteristics: | N (%) Participated in titration | N (%) Did not participate in titration | Difference |
|---|---|---|---|
| Gender M/ F | 26 (86%) / 4 (14%) | 27 (71%)/ 11 (29%) | $\chi^2$= 2.36 (p>0.05) |
| IQ Mean (SD) | 95.1 (9.6) | 95.06 (13.1) | t=0.14 (p>0.05) |
| Ethnicity: white /other | 23 (76.6%) / 7 (23.4%) | 31 (81.6%) / 7 (18.4%) | $\chi^2$=0.25 (p>0.05) |
| SES: < $20.000 | 11(36.7%) | 12 (31.5) | $\chi^2$=0.67 |
| $20.000 -40.000 | 6 (20%) | 6 (15.8%) | (p>0.05) |
| > $40.000 | 12 (40%) | 19 (50%) | |
| Age: Mean (SD) | 8.7 (1.49) | 9.3 (1.59) | t=1.70 p>0.05 |
| Handiness[2] R/L | 27 (90%) /3 (10%) | 31(81.6%) / 7 (18.4%) | $\chi^2$=0.94 (p>0.05) |
| Medication for ADHD: yes /no | 12 (40%) / 18 (60%) | 8(21.1%) / 30(78.9%) | $\chi^2$=2.90 (p>0.05) |
| ADHD subtype[3] | | | |
| Inattentive: | 4 (13.3%) | 14 (36.8%) | $\chi^2$=7.07 |
| Hyperactive : | 1 (3.3%) | 4 (10.5%) | (p<0.05)* |
| Combined: | 25 (83.3%) | 20 (52.6%) | |
| PP R+L+Both | 31.7 (5.7) | 32.17 (4.7) | t=0.36 (p>0.05) |
| PP Assembly | 24.88 (7.2) | 24.4(5.0) | t=0.31(p>0.05) |
| Word Naming | 51.1 (17.9) | 58.61 (18.3) | t=1.69(p>0.05) |
| Color Naming | 39.9 (10.5) | 41.26 (9.8) | t= 0.53 (p>0.05) |
| Color-Word | 25.6 (7.5) | 23.9 (6.8) | t=0.98(p>0.05) |
| Interference | -14.7(9.4) | -17.3 (8.4) | t= 1.24 (p>0.05) |

[2]Handiness - Assessed at the baseline (based on the hand child writes with);

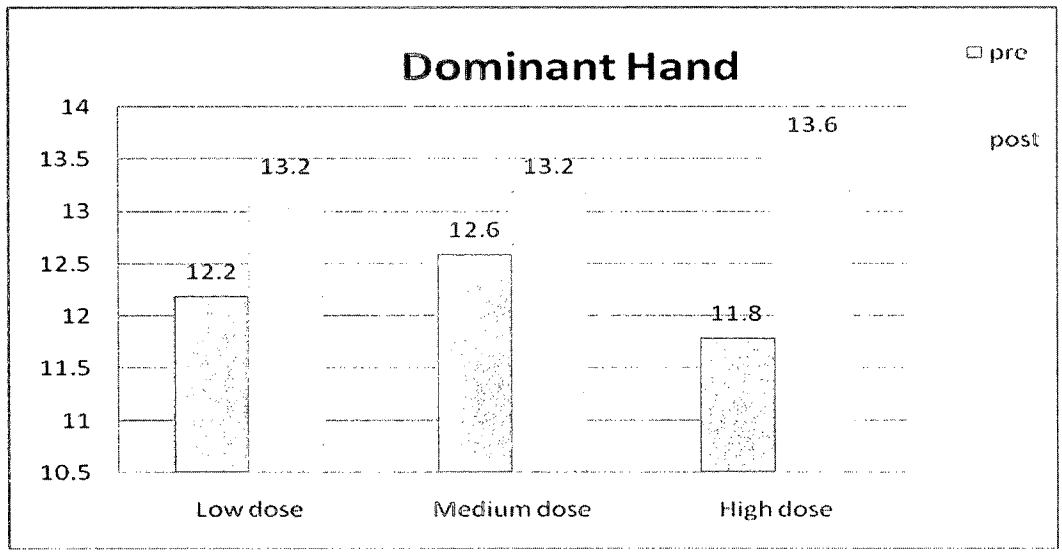
[3] Number of Items and Subtype of ADHD -Rated at the psychiatric evaluation by a clinical psychiatrist based on the DSM-IV.

Out of 30 children included in the analysis, 86% were boys and 14% were girls. Only one child met the criteria for the hyperactive subtype and three children were diagnosed with the inattentive subtype. The rest of the participants met criteria for the combined subtype of ADHD. The chi-square statistics was performed to assess whether the demographic characteristics of the titration sample differed from the baseline sample. Children who participated in the titration part of our study did not differ in terms of demographic characteristics from children who participated in the baseline part of the study. In terms of clinical characteristics, we found that within the subgroup of children who participated in the titration study, there were less children diagnosed with inattentive subtype ($p<0.05$).

*3.2.2 Effects of MPH on Motor Performance MPH: Purdue Pegboard*

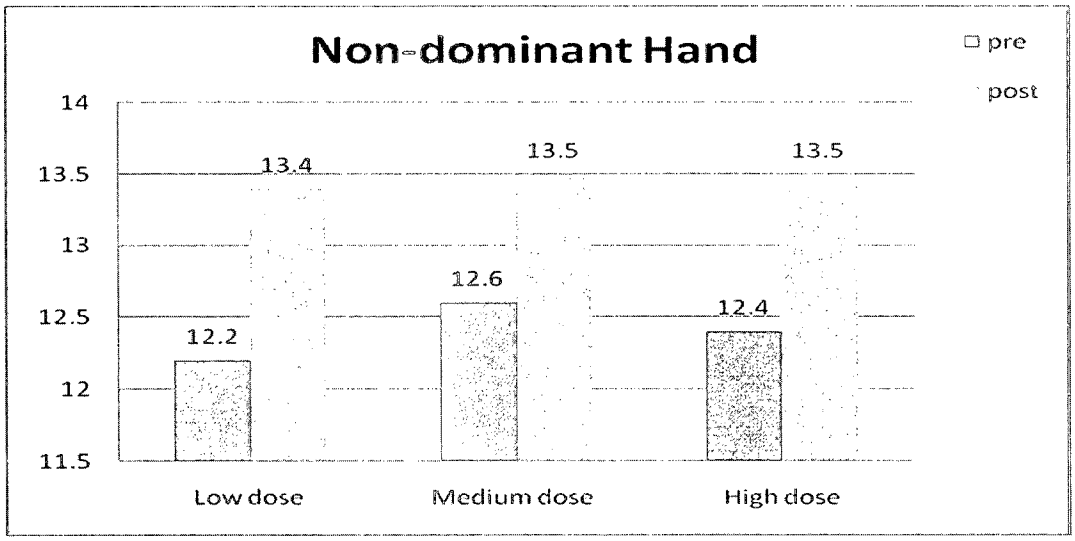
The following three figures (2– 4) show the means of the performance on different subtests of Purdue Pegboard Test before and after the administration of MPH.

**Figure 2:** Means of scores on Dominant Hand scale of the Purdue Pegboard before and after the 3 doses of MPH



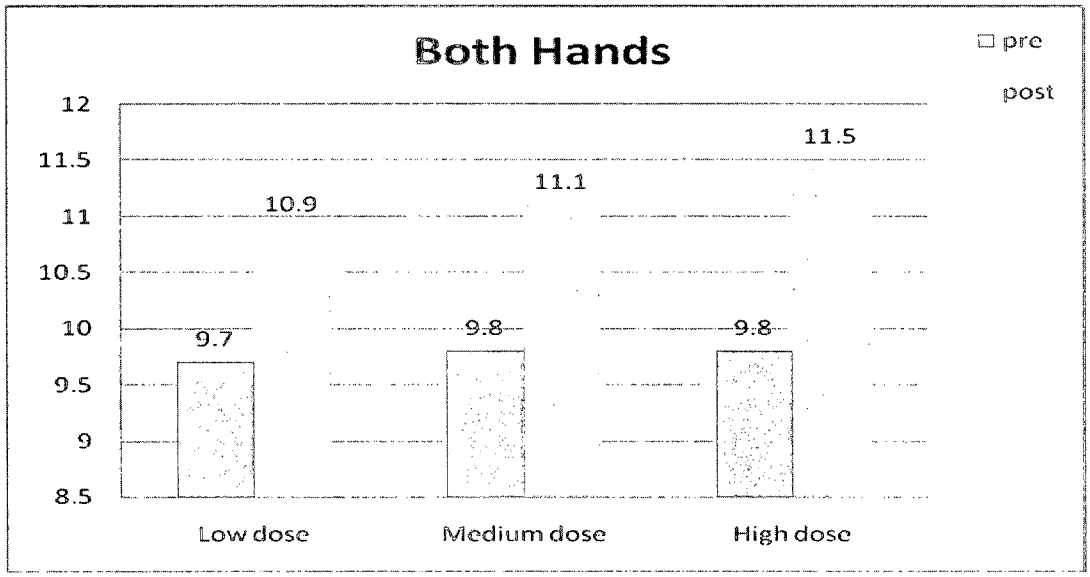

* **Low Dose** – Average Performance with Dominant Hand on Purdue Pegboard on low (0.3 mg/kg /day) dose of MPH. **Medium Dose** – Average Performance with Dominant Hand on Purdue Pegboard on medium (0.5 mg/kg /day) dose of MPH. **High Dose** - Average Performance with Dominant Hand on Purdue Pegboard on high (0.8 mg/kg /day) dose of MPH.

**Figure 3:** Means of scores on Non-Dominant Hand scale of the Purdue Pegboard before and after the administration of 3 doses of MPH



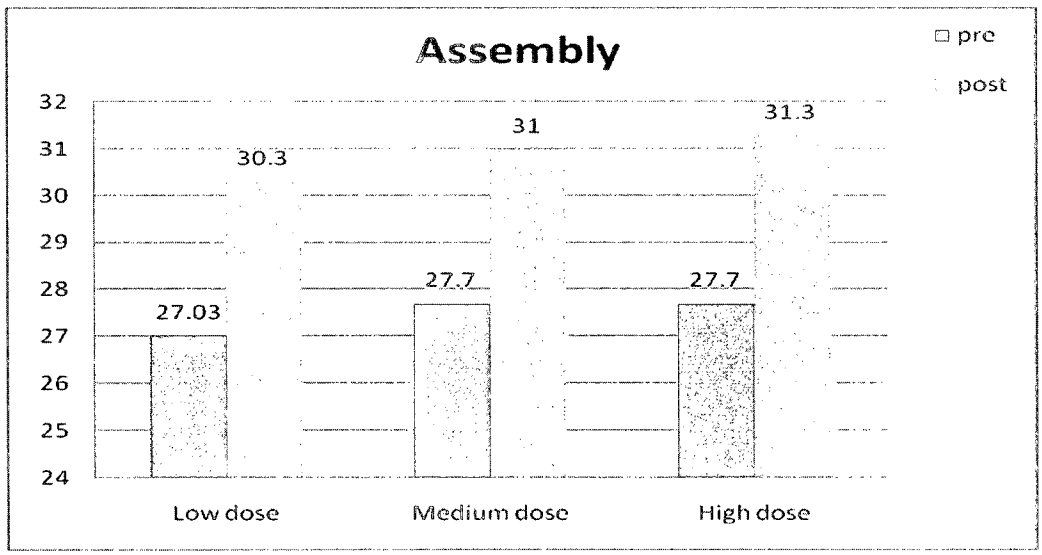

* **Low Dose** – Average Performance with Non-Dominant Hand on Purdue Pegboard on low (0.3 mg/kg /day) dose of MPH. **Medium Dose** – Average Performance with Non-Dominant Hand on Purdue Pegboard on medium (0.5 mg/kg /day) dose of MPH. **High Dose** - Average Performance with Non-Dominant Hand on Purdue Pegboard on high (0.8 mg/kg /day) dose of MPH.

**Figure 4:** Means of scores on the Both Hands subtest of the Purdue Pegboard before and after the administration of 3 doses of MPH




* **Low Dose** – Average Performance with Non-Dominant Hand on Purdue Pegboard on low (0.3 mg/kg /day) dose of MPH. **Medium Dose** – Average Performance with Non-Dominant Hand on Purdue Pegboard on medium (0.5 mg/kg /day) dose of MPH. **High Dose** - Average Performance with Non-Dominant Hand on Purdue Pegboard on high (0.8 mg/kg /day) dose of MPH.

**Figure 5:** Means of scores on the Assembly subtest of the Purdue Pegboard Test before and after the administration of the 3 doses of MPH




* **Low Dose** – Average Performance with Non-Dominant Hand on Purdue Pegboard on low (0.3 mg/kg /day) dose of MPH. **Medium Dose** – Average Performance with Non-Dominant Hand on Purdue Pegboard on medium (0.5 mg/kg /day) dose of MPH. **High Dose** - Average Performance with Non-Dominant Hand on Purdue Pegboard on high (0.8 mg/kg /day) dose of MPH.

The dose by treatment interaction effect of MPH on motor performance was analyzed using two-way within subjects ANOVA analysis, where treatment factor consisted of two levels, before and after the medication, and dose factor consisted of three levels, low, medium and high dose conditions. The results of the ANOVA analysis are presented in Table 6. For all the subscales of the Purdue Pegboard, there was no dose by treatment interaction ($p>0.05$), suggesting similar performance across all three doses of MPH.

**Table 6:** ANOVA analysis of dose and treatment effects on Purdue Pegboard scores.

| | Dose[1] : F(p) | Treatment[2] F (p) | Dose x Treatment F (p) |
|---|---|---|---|
| Dominant | 0.721 (0.403) | 64.75 (0.00)** | 0.682 (0.415) |
| Non-dominant | 0.368 (0.549) | 39.6 (0.00)** | 0.093 (0.762) |
| Both | 1.25 (0.30) | 49.01 (0.00)** | 1.14 (0.245) |
| Assembly | 1.085 (0.306) | 53.75 (0.00)** | 0.146 (0.705) |

[1] -Dose factor, has three level: low, medium and high doses; [2] - Treatment factor, has 2 levels: pre and post medication conditions ** - Significant ($p<0.0001$)

The treatment effect for Dominant Hand is significant across all three doses ($p<0.01$), indicating that performance on the post medication condition is significantly better than prior to the treatment.

Similar results were obtained for the Non-Dominant hand subtest; the treatment effect is significant across all three doses of MPH ($p<0.01$).

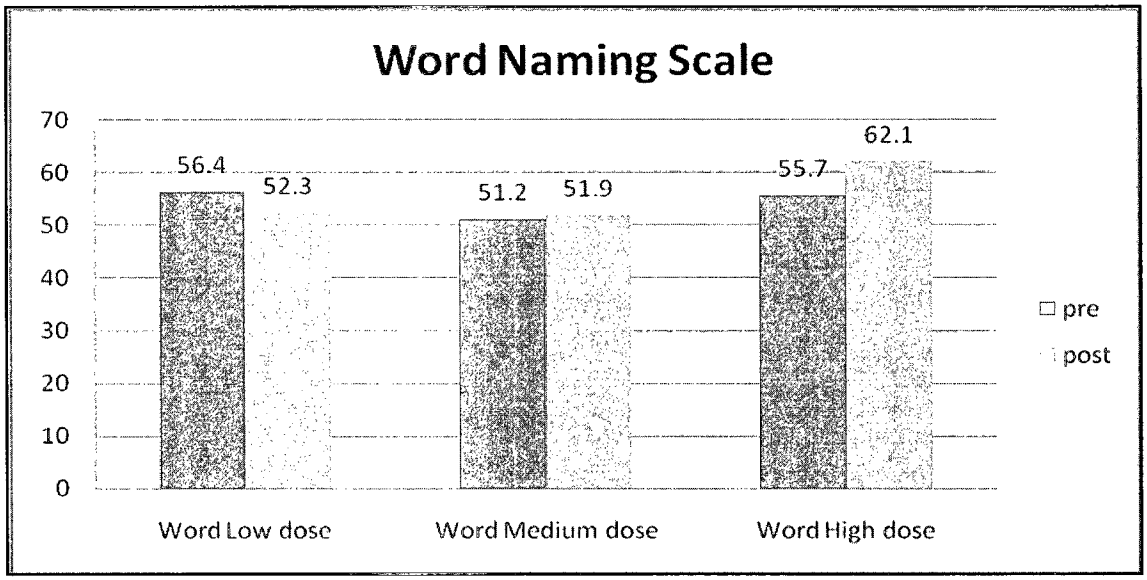
The results for the Both Hand Subtest of the Purdue Pegboard also indicate highly significant treatment effect for all three doses of MPH ($p<0.01$).

The repeated measures analysis performed for the *Assembly* scores revealed similar results of the same trend, indicting highly significant treatment effect of MPH on the speed of the performance ( $p<0.01$).

*3.2.3 Effects of MPH on the STROOP performance*

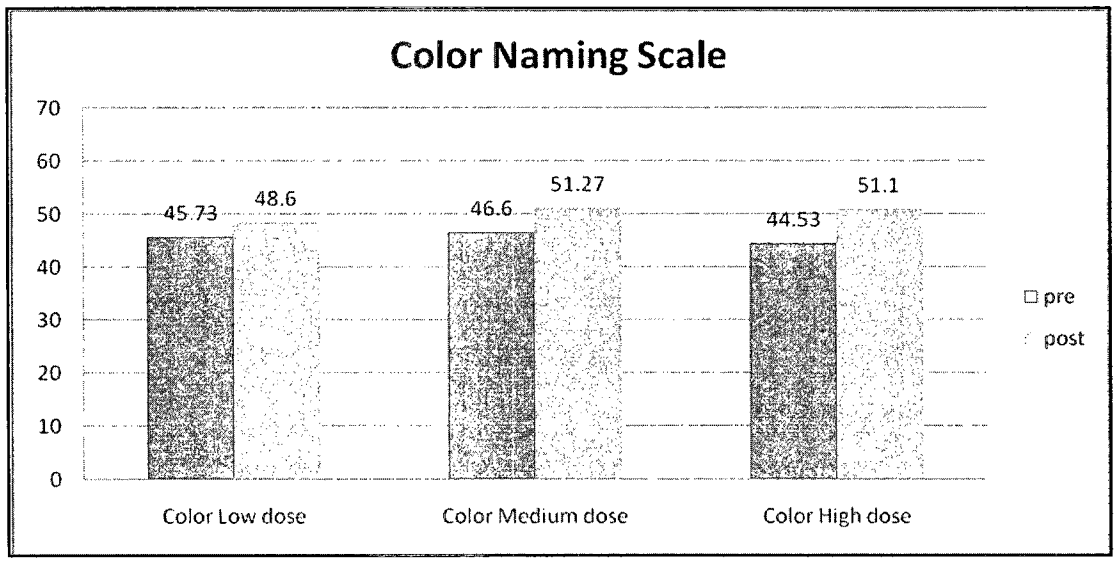
The Means of Scores on all subscales of the STROOP Color and Word test before and 60 minutes after the administration of each of the dose conditions are represented by the following figures *(Figures 6-8).*

**Figure 6** : Means of scores on Word Naming subscale of the STROOP before and after the administration of 3 doses of MPH



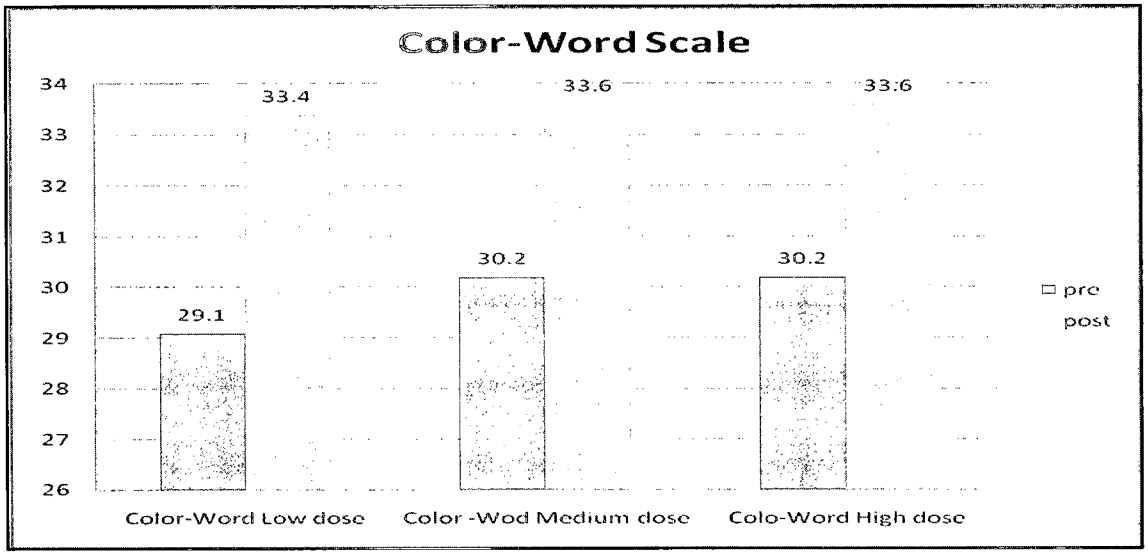

***Word Low Dose** – Average Performance on Word Scale of the STROOP on low (0.3 mg/kg /day) dose of MPH. **Word Medium Dose** – Average Performance on the Word Scale of the STROOP on medium (0.5 mg/kg /day) dose of MPH. **Word high Dose** - Average Performance on the Word Scale of the STROO on high (0.8 mg/kg /day) dose of MPH.

**Figure 7 :** Means of scores on Color Naming subscale of the STROOP before and after the administration of 3 doses of MPH



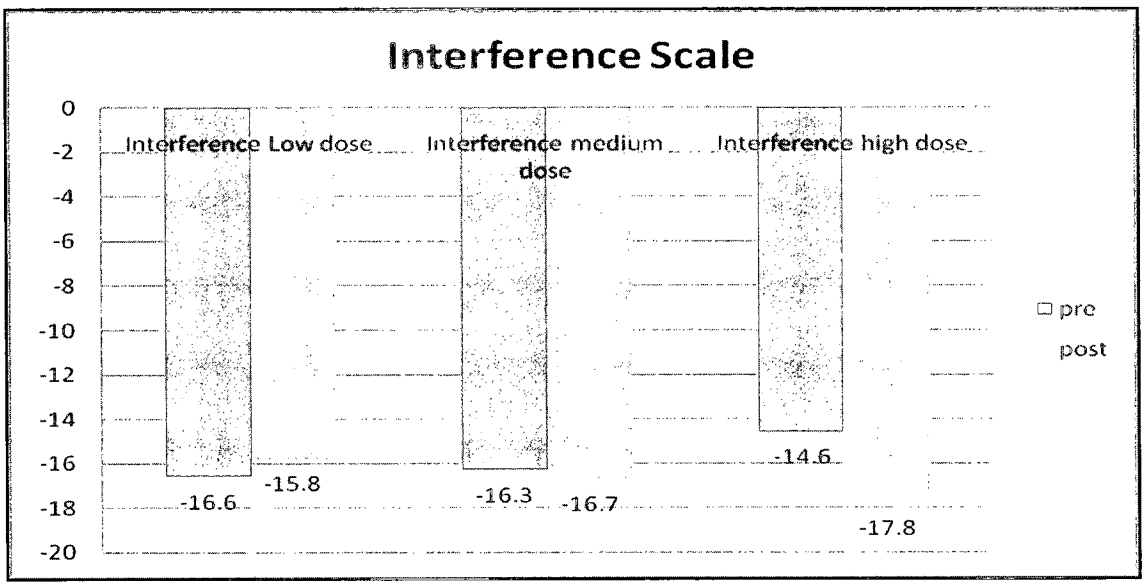

***Color Low Dose** – Average Performance on Word Scale of the STROOP on low (0.3 mg/kg /day) dose of MPH. **Color Medium Dose** – Average Performance on the Word Scale of the STROOP on medium (0.5 mg/kg /day) dose of MPH. **Color High Dose** - Average Performance on the Word Scale of the STROO on high (0.8 mg/kg /day) dose of MPH.

**Figure 8:** Means of scores on Color-Word subscale of the STROOP before and after the administration of 3 doses of MPH




***Color-Word Low Dose** – Average Performance on Color-Word Scale of the STROOP on low (0.3 mg/kg /day) dose of MPH. **Color –Word Medium Dose** – Average Performance on the Color-Word Scale of the STROOP on medium (0.5 mg/kg /day) dose of MPH. **Color-Word High Dose** - Average Performance on the Color-Word Scale of the STROOp on high (0.8 mg/kg /day) dose of MPH.

**Figure 9 :** Means of scores on Interference subscale of the STROOP before and after the administration of 3 doses of MPH




**Interference Low Dose** – Average Performance on Interference Scale of the STROOP on low (0.3 mg/kg /day) dose of MPH.

**Interference Medium Dose** – Average Performance on the Interference Scale of the STROOP on medium (0.5 mg/kg /day) dose of

MPH. **Interference High Dose** - Average Performance on the Interference Scale of the STROOP on high (0.8 mg/kg /day) dose of MPH.

The effect of MPH on Stroop performance was analyzed using two-way within subjects ANOVA analysis, where the treatment factor consisted of two levels: before and after the medication; the dose factor consisted of three levels: low, medium and high dose conditions. The results of the ANOVA analysis are presented in Table 7.

**Table 7:** ANOVA analysis of dose and treatment effects of MPH on STROOP scores.

| | Dose[1] : F(p) | Treatment[2] F (p) | Dose x Treatment F (p) |
|---|---|---|---|
| Word | 0.39 (0.8) | 50.6 (0.00)** | 1.1 (0.3) |
| Color | 0.37 (0.55) | 43.13 (0.00)** | 6.37 (0.02)* |
| Color-Word | 0.14 (0.87) | 25.29 (0.00)** | 0.44 (0.65) |
| Interference | 0 (0.99) | 0.7 (0.4) | 3.57 (0.035)* |

[1] -Dose factor, has three level: low, medium and high doses; [2] - Treatment factor , has 2 levels : pre and post medication conditions * - Significant at $p<0.05$; ** - Significant at $p<0.0001$

For the subscales that showed significant dose by treatment interaction, a Tukey's Post-hoc analysis was performed to examine on which level the factors were significantly different.

For the **Word Scores** of the STROOP C&W Test no dose effect, but a significant treatment effect was observed ($F = 50.5$ $p < 0.001$). No dose by treatment interaction was observed ($p>0.05$).

For the **Color Scores** of the STROOP C&W Test there was a significant dose by treatment interaction $F = 3.56$ ($p<0.035$). A post hoc t-test on the post-medication measures suggested that performance after the administration of the low dose was

significantly worse than performance after the medium dose ($p<0.05$), and almost significantly worse compared to post-high dose ($p<0.06$). However, the post hoc testing using the Tukey Honestly Significant Test (HSD) failed to confirm this difference.

For all three days there was a highly significant treatment effect associated with the administration of MPH $F=43.13$ ($p<0.001$).

For the **Color-Word Scores** of the STROOP C&W Test no dose effect, but a significant treatment effect was observed ( $F=25.29$ $p<0.001$). No dose by treatment interaction was observed ($p>0.05$).

For the **Interference Score,** a two-way repeated ANOVA analysis revealed significant dose by treatment interaction ($F = 3.57$ $p<0.05$). Tukey HSD post-hoc analysis revealed that the treatment effect is observed only at the high dose of medication ($F = 6.23$, $p <0.01$).

### *3.2.4 Structure of motor and verbal response*

We further examined the stability of the factors that were determined in the first part of the study (see part 3.1.4).

The results of the Principle Component Analysis introduced at the baseline stage of our study confirms the stability of the loading scales for each factor as represented by Table8.

**Table 8:** Factor Loadings (PCA) at the six different observation times

| | Pre Low | | Post Low | | Pre Medium | | Post Medium | | Pre High | | Post High | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | M-C[11] | Int[12] | M-C | Int | M-C | Int | M-C | Int | M-C | Int | M-C | Int |
| Word[1] | .87 | -.14 | .894 | -.07 | .89 | -.12 | .90 | .01 | .91 | -.02 | .86 | .05 |
| Color[2] | .88 | -.08 | .89 | .14 | .88 | -.16 | .89 | .10 | .86 | -.00 | .89 | .30 |
| C-W[3] | .55 | .74 | .61 | .75 | .66 | .62 | .67 | .66 | .03 | .72 | .61 | .78 |
| Inter[4] | -61 | .75 | -.57 | .78 | -.44 | .88 | -.45 | .81 | -.57 | .74 | -.69 | .60 |
| Dom[5] | .91 | .10 | .79 | .08 | .83 | .25 | .89 | .01 | .82 | .14 | .88 | -.05 |
| N-D[6] | .83 | .10 | .80 | -.09 | .80 | -.05 | .84 | -.17 | .86 | .07 | .85 | -.20 |
| Both[7] | .84 | .00 | .86 | -.05 | .86 | -.07 | .81 | -.15 | .88 | .10 | .89 | -.08 |
| Asm[8] | .79 | .10 | .78 | -.03 | .81 | .16 | .83 | .08 | .78 | .19 | .82 | -.11 |
| Eig[9] | 5.2 | 1.2 | 4.9 | 1.2 | 4.9 | 1.2 | 5.0 | 1.2 | 4.6 | 58.3 | 5.3 | 1.2 |
| Var[10] | 64.8 | 14.6 | 61.3 | 15.1 | 61.6 | 16.2 | 63.0 | 14.4 | 1.5 | 18.2 | 66.6 | 14.0 |

[1]Word - Word Naming Score of the Stroop; [2]Color - Color Naming Score of the Stroop; [3] C-W – Color Word Score of the Stroop; [4] Inter – Interference Score of the Stroop; [5] Dom- Dominant Hand of the Purdue Pegboard [6] N-D- Non-Dominant hand score of the Purdue Pegboard; [7] Both- Both hands score of the Purdue Pegboard; [8] Asm- Assembly score of the Purdue Pegboard; [9] Eig- Eigenvalues for the Principle Components; [10]Var- percent of variance; [11]MC – Motor cognitive factor ; [12]Int – Interference factor

Our results indicate that the loading of the Motor-Cognitive Factor is consistent in all six instances, and it consists of all Purdue Pegboard scales, Word Naming and Color Naming Scales of the STROOP. Interference factor is consistently loaded with the Interference score, yet the Color-Word score is less consistent, thus it was not considered as a main factor component for the next step of our analysis. The Interference Score loading on the second factor is consistent in all six times and will be considered only as a component of the second factor; it will be referred to as an Interference Factor. The two-way repeated measures ANOVA was performed in order to assess the characteristics of the response to three different doses of MPH according to the two determined factors. Our analysis suggests that there is a significant treatment effect ($F=130.2$, $p<0.01$) but no dose by treatment interaction for the Motor Cognitive Factor.

For the Interference Factor that is consistently loaded with the Interference Score of the Stroop (consistently over 0.7), two-way repeated ANOVA analysis revealed significant dose by treatment interaction ($F = 3.57$ $p<0.05$). Tukey HSD Post-hoc analysis reveals that the treatment effect is observed only at the high dose of medication ($F = 6.23$, $p <0.01$).

### *3.2.5 Effects of MPH on behavior during academic task: RASS*

The means of scores obtained on different subscales of the Restricted Academic Situation Scale during the time children were performing math problems matched to their academic level prior to and 2 hours after the administration of MPH on three different days, are represented in the following Figures *(8-9)* according to the factors suggested by Karama (Karama et al., 2008 in press). As suggested by this work, the RASS is decomposed into two main factors: Motor activation (MA) contributed mainly by the fidgeting item of the

RASS, and Task Disengagement (TD) loaded by " Off task", " Playing with Object" and " Out of Seat " scales. This factor structure is reproduced in the present sample of patients participating in the titration trial (Table 9).

**Table 9:** Factor Loadings (PCA) for the RASS scales at six different times.

| | Pre Low | | Post Low | | Pre Medium | | Post Medium | | Pre High | | Post High | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | TD[8] | MA[9] | TD | MA | TD | MA | TD | MA | TD | MA | TD | MA |
| Off Task[1] | 9.2 | 1.4 | 9.1 | .06 | .93 | -.08 | .91 | .10 | .89 | .17 | .76 | -.40 |
| Fidg[2] | -.46 | .67 | -.12 | .79 | -.52 | .5 | -.24 | .80 | -.55 | .72 | .23 | .84 |
| Vocal[3] | .70 | .41 | .74 | .20 | .67 | .47 | .85 | .07 | .66 | .45 | .76 | .05 |
| Pl. obj.[4] | .94 | .20 | 9.2 | .19 | .93 | -.17 | .84 | -.28 | .90 | .17 | .87 | -1.1 |
| Off seat[5] | .45 | -.67 | .49 | -.66 | .21 | -.83 | .44 | .63 | .62 | -.36 | .49 | .36 |
| Eig[6] | 2.6 | 1.3 | 2.4 | 1.4 | 2.5 | 1.2 | 2.5 | 1.1 | 2.7 | 1.0 | 2.2 | 1.0 |
| Var[7] | 52.9 | 22.8 | 48.6 | 22.9 | 49.9 | 24.0 | 50.2 | 22.7 | 54.8 | 18.4 | 44.2 | 20.2 |

[1]Off Task – Off Task score on the RASS; [2]Fidg – Fidgeting score on the RASS; [3]Vocal – Vocalizing Scale of the RASS; [4] Pl. obj. – Playing with object scale of the RASS; [5] Off seat – Our off seat scale of the RASS; [6] Eig- Eigenvalues for the Principle Components; [7]Var- percent of variance; [8]TD – Task Disengagement factor ;[9]Int – Interference factor

The effects of MPH on behavioral domain as measured by RASS was further analyzed using two-way within subjects ANOVA analysis, where treatment factor consisted of two levels: before and after the medication, and dose factor consisted of three levels: low, medium and high dose conditions. Tukey's Honestly Significant Test was performed to decompose the effect of the dose factor, when the interaction was found significant. First, the analysis was performed between the two behavioral components

*Motor Activation* and *Task Disengagement* as proposed by Karama (Karama et al., in press).

Motor Activation is a dose by treatment interaction F = 3.78 (p =0.03). There is a dose (F = 4.25 p = 0.02) and treatment effect (F= 7.65 p = 0.01). A Tukey Honestly Significant difference post hoc analysis revealed that there is a difference across doses on post medication (F = 6.61; p = 0.019), but not before medication ( p>0.05).

Post hoc testing (using Tukey HonestlySignificant difference test) reveals that post-medication performance on high dose is significantly different from the performance on post- low dose condition ($p < 0.05$) as well as from the post-medium dose $p < 0.01$. There is no difference between the performance on post-low and post-medium conditions (p >0 .05).

For the Task Disengagement, two-way repeated measures analysis of variance did not reveal a dose by treatment interaction (p>0.05). There is a significant treatment effect (F = 74.36 p <0.001), suggesting a decrease of task disengagement behavior following the administration of methylphenidate. No dose by treatment interaction was revealed.

### *3.2.6 Rate of Improvement*

Many studies examining the effects of medication have used a difference between post and pre-medication performance as a measure of improvement. For the overall analysis of the change produced by each dose formulation, the delta score was computed for each factor as a difference between the post-medication score and pre-medication score.

$$\Delta = \text{Post MPH Score} - \text{Pre MPH Score}$$

The results of our analysis of the change rates for the two previously described dimensions of motor-cognitive and interference factors are represented by Table 8.

One way, ANOVA indicates no significant difference in the rate of improvement for the Motor-Cognitive Factor ($F = 1.9$, $p>0.05$). For the Interference Factor, there is a significant difference between the improvement associated with three doses of MPH ($F = 3.56$, $p<0.05$). The post hoc Tukey HSD test reveals that the improvement associated with the high dose of MPH is larger than the improvement associated with the low and medium doses ($p<0.05$). There is no difference between the low and medium doses in terms of the change of the interference control.

**Table8:** ANOVA (Tukey HSD post hoc) by cognitive factors:

| Delta (improvement) | Mean difference (St.Error) | F (p ) |
|---|---|---|
| ΔMotor-Cognitive [1] Low Dose | 13.9 (12.7) | F=1.9 (0.15) |
| Δ Motor-Cognitive [1] Medium dose | 16.6 (15.0) | |
| Δ Motor-Cognitive[1] High dose | 20.8 (14.1) | |
| Δ Interference[2] Low dose | 0.97 (1.3) | |
| Δ Interference[2] Medium dose | 0.13 (1.1) | 3.56 (0.04)* |
| Δ Interference[2] High dose | -3.2 (1.5) | |

[1]Motor-Cognitive – A sum of all Purdue Scores and score on Word naming and Color naming of the STROOP; [2]Interference– Interference score of the Stroop

Overall behavioral improvement as measured by RASS Total Score shows significant dose effect ($F= 5.27$ $p<0.05$). The post hoc Tukey HSD test reveals that the improvement is significantly higher after the administration of the high dose of MPH compared to the low ($p<0.05$) and medium doses of MPH ($p<0.01$). Our results indicate that there is a significant difference in the rate of the change associated with high and

low doses of MPH on the measures of the Motor Activation dimension ( F = 3.78, p<0.05), but not on the Task Disengagement (p<0,05). The post hoc Tukey's HSD analysis reveals that the improvement of motor activation behavior (decrease) is significantly larger after the administration of the high dose of MPH compared to the low dose of MPH.

We examined the improvement rates using the one-way analysis of variance for two dimensions, Motor Activation and Task Disengagement.

**Table 8:** The mean change in Motor Activation, Task Disengagement and overall behavior from pre to post-administration for three doses of MPH.

| Delta (improvement) | Mean difference (St.Error) | F (p ) |
|---|---|---|
| ΔMotor Activation [1] Low dose | -4.433 (6.7) | |
| Δ Motor Activation [1] Medium dose | -5.33 (6.13) | 3.78 (0.029)* |
| Δ Motor Activation [1] High dose | -6.467 (7.9) | |
| Δ Task Distractibility[2] Low Dose | -5.9 (1.1) | |
| Δ Task Distractibility[2] Medium Dose | -4.8 (1.1) | 2.4 (0.096) |
| Δ Task Distractibility[2] High Dose | -8.3 (1.3) | |
| ΔTotal Score on RASS Low Dose* | -25.5 (4.6) | |
| Δ Total Score on RASS Medium Dose* | -21.9 (4.4) | 5.27 (0.008)** |
| Δ Total Score on RASS High Dose* | -38.5 (4.8) | |

[1] ΔMotor-Activation – a change on the Motor Activation for each dose (Post – Pre)

[2] Δ Task Distractibility – a change on the Task Distractibility for each dose (Post – Pre)

The one-way analysis of variance indicates that there is a significant change in the rate of improvement produced by three different doses of MPH in Motor Activation. As revealed by Tukey's HSD post hoc test there is a significantly larger decrease of Motor Activation from pre to post-administration of the high dose compared to the change from

pre to post-administration of two other doses of MPH ( $p<0.05$). There is no significant difference between low and medium dose conditions in the rate of produced improvement ($p>0.05$).

The overall behavior as measured by total scores on the RASS was significantly better on the high dose compared to medium dose ($p<0.01$) as well as compared to low dose ($p<0.05$).

## CHAPTER IV: DISCUSSION

The goal of the present study was to explore the characteristics of motor and verbal performances without medication and in response to three different doses of MPH in children diagnosed with ADHD. Besides motor and verbal measures, an ecological measure of behavior (RASS) was used to assess behavioral response to three different doses of medication.

### 4.1 Motor and Verbal performance in children diagnosed with ADHD

During the first part of the study children diagnosed with ADHD performed Purdue Pegboard and Color and Word Stroop Tests while they were off medication for at least seven days. We first analyzed the results of each domain, and then explored the characteristics of the association between motor and verbal domains of cognitive performance.

#### *4.1.1 Characteristics of motor performance in children diagnosed with ADHD*

Only a few small studies have examined the motor performance in ADHD children using Perdue Pegboard as an assessment tool. While suggesting that there are more children diagnosed with ADHD who perform poorly on the test than in the control

group, studies fail to find statistical differences between the ADHD and control groups. Nevertheless, studies indicate pronounced differences between the control group and children diagnosed with both ADHD and Developmental Coordination Disorder (Flapper, Houwen, & Schoemaker, 2006). Overall, it has been suggested that children and adults diagnosed with ADHD are characterized by a certain degree of motor slowness and motor coordination problems (Fliers et al., 2008; Feng et al., 2007; Pitcher et al., 2003; Piek et al., 1999).

Consistent with these findings, analysis of our data provides some indications of motor slowness in children diagnosed with ADHD. Our results suggest that the scores of the performance on the dexterity task are distributed differently in the sample of children diagnosed with ADHD than it would be expected in healthy controls. We observed that on the simple conditions of the Purdue Pegboard test (one hand at time and simultaneous movements of hands) there are more children who perform considerably worse than the average (2 SD below the age mean). In our sample, there were no children who performed considerably better than average (2 SD over the age mean).

However, this present study did not have a control group and normative data was only available from the Purdue Pegboard Scoring Manual, thus these results can be only seen as preliminary and need further investigations.

Studies of motor performance in clinical populations have linked dexterity deficiencies as measured by Purdue Pegboard to poor social functioning in schizophrenia patients (Lehoux et al., 2003) and poor psychosocial outcomes in Tourettes patients (Bloch, Sukhodolsky, Leckman, & Schultz, 2006). It is thus possible that children with poor motor coordination and slow motor performance might constitute a separate

subgroup of ADHD. Furthermore, it was recently suggested that some components of the motor coordination dysfunction might have a genetic component, since similar difficulties are observed in non-affected siblings of ADHD children while performing motor coordination tasks (Tracking Task) (Rommelse et al., 2008; Rommelse et al., 2007).

Consistent with previous findings (Fliers et al., 2008; Rommelse et al., 2007), our analysis did not reveal gender differences in terms of performance on motor tasks in children diagnosed with ADHD. It is surprising, since studies of normal populations consistently report better performance in girls versus boys (Brito & Santos-Morales, 2002; Mathiowetz, Rogers, Dowe-Keval, Donahoe, & Rennells, 1986) and this gender difference persists into adulthood (Bryden & Roy, 2005; Schmidt, Oliveira, Rocha, & Abreu-Villaca, 2000). However, it is possible that we failed to find gender differences because of the counteraction of different factors; it has been reported that children with the inattentive subtype have more difficulties on motor tasks (T. M. Pitcher, Piek, & Hay, 2003) and, overall, there are more girls than boys8 who are diagnosed with the inattentive subtype of ADHD in clinically referred samples (Biederman et al., 2002). Further investigation of gender specific differences in children diagnosed with ADHD is needed.

It has been reported that children diagnosed with the inattentive subtype of ADHD perform worse on motor skills than children diagnosed with combined and hyperactive subtypes of ADHD (T. M. Pitcher, Piek, & Hay, 2003; T. P. Pitcher, J., 2000). However, other studies fail to confirm these findings (Meyer A.; Sagvoklen, 2006). In our study, we did not observe subtypes of ADHD that did not differ in terms of their performance on the motor dexterity task.

*4.1.2 Characteristics of verbal performance in children diagnosed with ADHD*

There is a long history of research of the Stroop effect; however, there is an ongoing controversy about the STROOP specific deficit in the ADHD population. A recent meta-analysis of 17 independent studies by Mourik et al., (Mourik, Oosterlaan, Sergeant, 2005) examining the performance on the Stroop in subjects diagnosed with ADHD, indicated that they perform more poorly on word-naming and on color-naming than healthy controls. Interestingly, the results for the Interference Score are less consistent and depend on the calculation method. For the studies that used the same calculation method, as in the present study (color word minus color score), no differences were found between ADHD groups and normal control groups. The work by Schwartz and Verhaeghen, (Schwartz and Verhaeghen, 2008) that performed a meta-analysis of 25 studies examining Stroop confirmed that there is no difference between ADHD and normally developing subjects on Interference Score.

The inconsistencies are increased by the differences in the computation of Interference Score (Schwartz and Verhaeghen, 2007) and types of the Stroop task used. For example, Bush et al., (Bush et al., 2008) used counting Stroop, Smith et al.( Smith et al., 2006) used motor Stroop task, and Tannock et al. (Tannock, Martinussen , Frujters, 2000) used verbal version of the task. Recent brain imaging studies confirm that there are differences in brain activation specific to ADHD, such as lower activation value of anterior cingulated cortex, basal ganglia, insula and cerebellum during the incongruent condition in ADHD children compared to controls (Zang et al.,2005). Interestingly, brain activation of subcortical structures while performing naming tasks was larger in the for ADHD children compare to controls (Zang et al.,2005).

Our results indicate that there is a color-naming deficit in children diagnosed with ADHD. Children name colors slower than normally developing children. These findings are consistent with previously reported deficit of color discrimination in children diagnosed with ADHD (Banaschewski et al., 2006; Tannock and Banaschewski, 2006, Roesner et al., 2008; Li et al., 2008). We also observed slower than normal naming of colors in the incongruent condition; however, there was no difference with the normative data in Interference Score.

Our results provide some indication that the performance of children with ADHD does not differ from the normative data on the Interference Score. However, this result should be further examined since we did not have a control group and the normative data from the Stroop Manual was used for the examination of the differences.

Consistent with previously reported findings (Rucklidge and Tannock, 2002), we did not observe gender differences in the performance on STROOP. In our study we did not observe any differences in the performance of different clinical subtypes of ADHD.

*4.1.3 Association between the measures of speed in motor and verbal domains*

Given that children diagnosed with ADHD were reported to perform slower than their normally developing peers on both verbal (Tannock, Martinussen, & Frijters, 2000) and motor tasks (Flapper, Houwen, & Schoemaker, 2006), we explored the relationship between the speed of motor and verbal performance. Our results indicate strong association between the speed of word naming and color naming in verbal domain and the speed of pin placing in motor domain. We can suggest that both naming on the STROOP and pin placing on Purdue Pegboard require similar action: quick automatic response. Based on our results we further suggest that simple motor task action (pin placing) and

simple verbal action (word and color naming) can be viewed as one factor. We believe that this factor can be described as a simple motor-cognitive action and is observed in performance requiring fast automatic response in either the motor or verbal domain. Our results align with the recently proposed idea that deficit in motor timing is a viable endophenotypic candidate of ADHD (Rommelse et al., 2008). We suggest that the fast automatic motor-cognitive action component can be seen as a separate dimension of executive functioning and is apparent in at least two different modalities, verbal and motor.

Our results side with the idea that there might be a common neurobiological mechanism responsible for the quick automatic response in both fine-motor and verbal-naming domains. This idea is supported by the fMRI studies indicating that there is a hypoactivation of similar brain structures (mesial prefrontal cortex) during motor timing (Bush et al, 1999) and Stroop tasks (Rubia et al., 1999) compared to healthy controls. Furthermore, it is possible that there are genetic commonalties for the deficits observed in both modalities. It has been reported that non-affected siblings of children diagnosed with ADHD perform worse than healthy controls on motor tasks (Rommeise et al., 2007) and on the STROOP task (Seidman, Biederman, Monuteaux et al., 2000).

Our analysis suggests that interference control constitutes a separate factor of executive functioning that cannot be explained by the speed of performance on simple tasks. These results go in line with the recent neuro-imaging findings showing that brain activation during the performance of tasks requiring interference control is different compared to simple tasks (DeSoto, Fabiani et al., 2001), and the level of activation during the interference task is lower in ADHD subjects compare to controls (Zang et al., 2005).

As discussed in the following part, the dose response to treatment might have distinct characteristics according to proposed dimensions.

**4.2 Dose effect of MPH on cognition and behavior**

During the second part of the study, children diagnosed with ADHD underwent testing on three consecutive days prior to and 60 minutes after the administration of three different doses of MPH ( 0.3; 0.5 and 0.8 mg/kg/day in a bid formulation). The Purdue Pegboard, Color and Word Stroop Tests and Restricted Academic Situation Scale were used on each of the six testing conditions.

*4.2.1 Dose effect of Methylphenidate on the motor-cognitive action*

The model proposed by Rapport and Kelly (Rapport and Kelly,1991) based on their review of the studies analyzing dose effects of MPH on cognitive functions suggests that automatic processing has optimal response on low doses of MPH (0.2-0.4 mg/kg day). According to their model, the response levels off at medium doses and then deteriorates at higher doses. The authors further suggest that tasks that require slow processing and increased effort such as behavioral inhibition and planning may show a more linear dose response curve with optimal improvements at higher doses of MPH (0.7 – 0.9 mg/kg).

As previously discussed, analysis of the motor and verbal measures suggest that simple motor cognitive action constitutes a specific dimension of the executive functioning. Principal Component Analysis for each testing condition (pre and post-medication on three dose formulations) indicates that the motor-cognitive factor is

consistently loaded by scores on simple motor tasks (subtests of the Purdue Pegboard) and simple verbal tasks (Word naming and Color naming).

Our results suggest that there is an effect of treatment with MPH on the motor-cognitive domain. We observed significant improvement of the scores on each of the components of this factor and global improvement of the factor in association with the treatment with MPH. Contrary to the Kelly and Rapport model, we did not observe dose effect of Methylphenidate on the motor-cognitive performance. We suggest that the optimal performance is achieved with low doses of MPH and the increase of the dosing does not lead to further improvement.

We did not observe any deterioration of the performance on simple tasks after the administration of high doses of MPH.

We suggest that motor-cognitive factor might be a valuable measure of simple cognitive mechanisms. We further suggest that this simple motor-cognitive function is improved by treatment with MPH, yet it is not sensitive to the increase of the dosing within clinically tolerable doses.

### *4.2.2 Dose effect on Interference Control*

As previously discussed, analysis suggests that interference constitutes a specific dimension of the performance. Principal Component Analysis model at each of the six times of testing indicates that Interference Control is a distinct factor that is consistent across all testing times (pre and post-medication on three dose conditions). The meta-analysis of studies examining the performance of children diagnosed with ADHD by

Lansbergen et al, (Lansbergen, Kenemans, & van Engeland, 2007) suggests that interference control is impaired in children and adults diagnosed with ADHD.

As previously discussed, it has been suggested that there is a specific brain dysfunction associated with the STROOP task in the ADHD population. The activation volume of the prefrontal cortex in both the neutral and interference conditions in ADHD children was smaller than in healthy controls. This difference tends to decrease with the administration of MPH (Zang et al., 2005).

Contrary to the finding of Bedard et al, (Bedard , 2002; Zang et al, 2005), who failed to find an effect of MPH on the interference, we suggest that Interference Control improves with the administration of MPH and this improvement is specific to a high dose of MPH. However, we used a slightly higher dose of MPH than in the study by Bedard (Bedard et al., 2002), where average high dose was under 0.7 mg/kg/day. The change in interference occurs at higher doses of MPH.

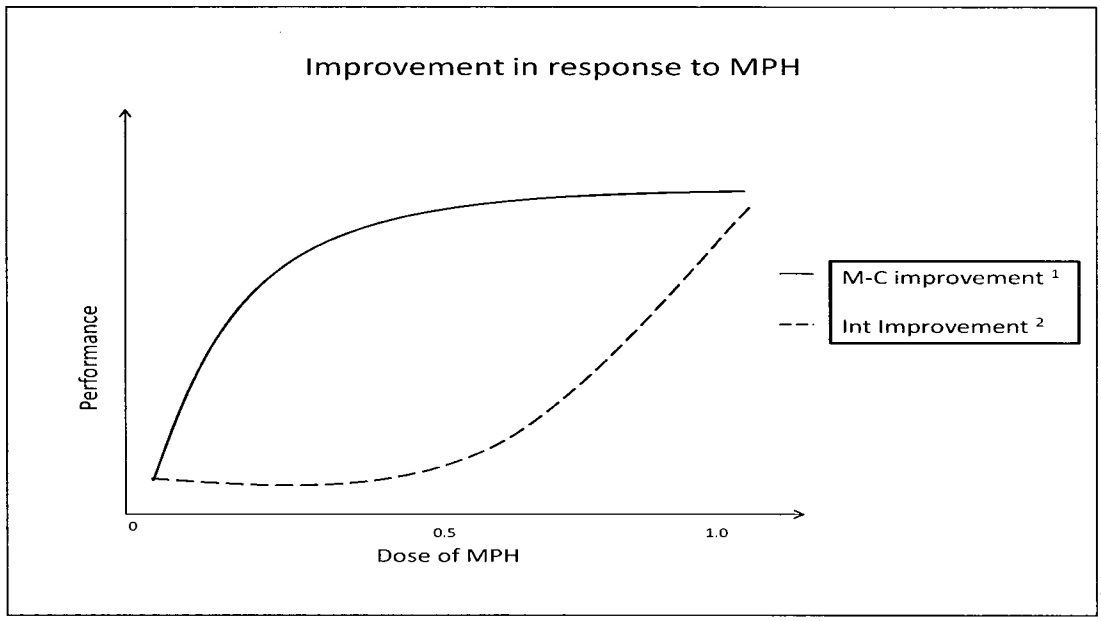
These results go in line with our assumption that the Interference Score reflects a complex measure that is distinct from other scales of the Stroop. This finding is important, since studies often do not report Interference Score, basing the analysis on Color-Word scale.

Overall our results did not support the model of response proposed by Rapport and Kelly (Rapport and Kelly, 1991). They suggested that the response on simple, automatic tasks will be observed on low doses whereas the improvement on more complex tasks is observed on higher doses (*see Figure1, p. 21).* However, contrary to the proposed inverted U shape of the response curve (Rapport and Kelly, 1991), we did not observe

deterioration in the speed of the performance following the administration of a high dose of MPH.

Our results support our original hypothesis of strong association between simple tasks that require quick automatic response. Furthermore the characteristics of the dose response are similar on these tasks and seem to constitute a unique dimension of cognitive functioning. We suggest that the characteristics of response to three different doses of MPH in the cognitive domain depend on the complexity of the task. Based on our results, we suggest that the simple motor cognitive response improves on low doses of MPH with no additional improvement on higher doses while complex task benefits from higher dosing (*Figure 12*). Contrary to our hypothesis and prediction made by Rapport and Kelly (Rapport and Kelly, 1991), we did not observe deterioration of performance on simple tasks of the STROOP such as word naming and color naming with the increase of dose of MPH.

**Figure 10:** Dose effect of MPH on Motor -Cognitive action and on the Interference Control.




[1]M-C – Motor-cognitive performance as measured by the sum of Purdue Pegboard Scales and Stroop Word Naming and Color Naming Scales

[2]Int – Interference control as measured by the Interference score of the Stroop Color and Word Test.

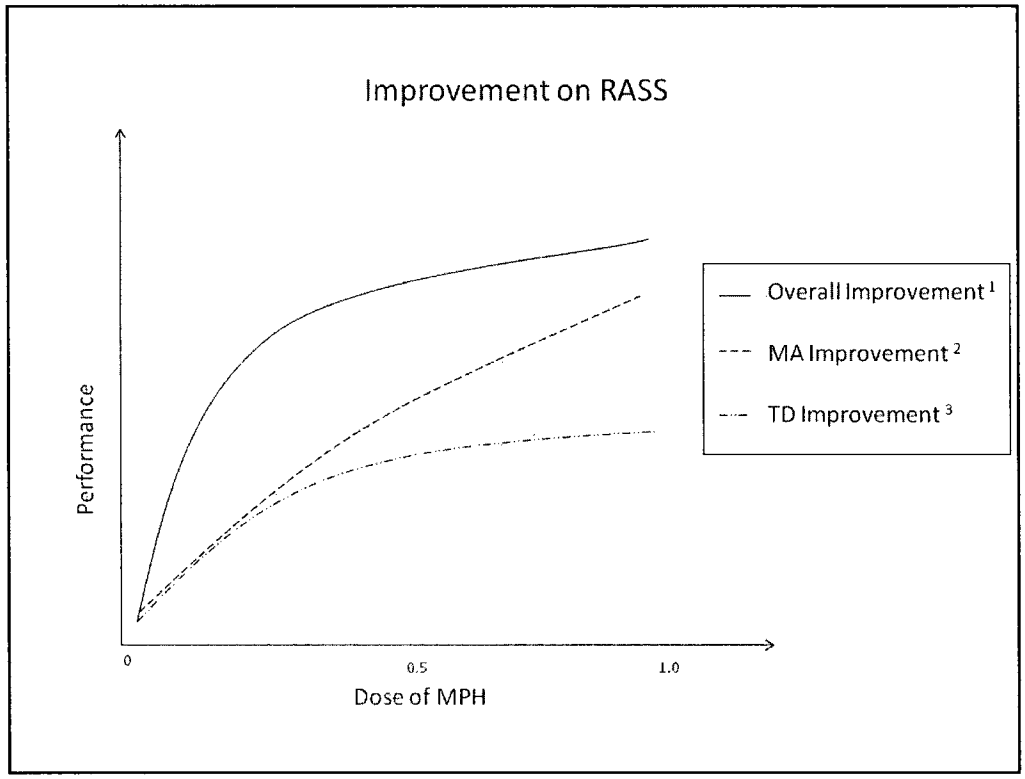
Overall, our analysis suggests that there are two distinct factors associated with the performance on Purdue Pegboard and Stroop Color and Word Test: Motor-cognitive Factor and Interference Factor. These two dimensions are characterized by different dose response curves.

*4.2.3 Dose effect of MPH on behavior during academic task.*

It has been consistently reported that there is a linear effect of MPH on behavior during academic tasks (Ex: Sprague, 1977). Consistent with those findings, our results suggest that an increased dose of MPH leads to a gradual improvement in overall behavior during academically relevant tasks as measured by Total Score of the RASS.

As it was recently suggested by the work of Karama et al., (Karama et al., in press) the behavior during academic tasks can be analyzed according to two main dimensions: Motor Activation and Task Distractibility. We found that these two dimensions differ in terms of dose response to MPH. While Motor Activation decreases gradually as the dose increases, the Task Disengagement decreases with treatment but does not depend on the dosing of MPH. We suggest that, whereas the improvement in MA will have a mostly linear shape, the improvement on TD behavior will have more fluctuations at lower doses, and will lead to an improvement the higher doses (Figure 13).

**Figure 11:** Dose-effect of MPH on Motor Activation, Task Disengagement and Overall behavior during performance of an academic task.




[1] Total Score – Overall behavior measured by the Total Score on RASS; [2]MA- Motor Activation measured by the *Fidgeting* Score on RASS; [3]TD – Task Distractibility measured by the *Off Task*, *Playing with Object* and *Out of Seat* Scores on RASS

Our findings provide further support to the work by Karama et al., (Karama et al., 2008) suggesting that Motor Activation and Task Distractibility might constitute two different dimensions of the behavior.

Overall, we suggest that the characteristics of the dose response are specific to the domain being measured. While Motor Activation decreases as the dose increases, the motor-cognitive performance reaches optimal level at low doses and does not ameliorate with the increase of dosing. We further suggest Interference Control, which is a more complex measure, only improves at higher dose of MPH.

These findings contribute to the idea that response to MPH may be a complex phenotype and that different behavioral and cognitive traits relevant for ADHD may present different profiles of response to methylphenidate.

**Strengths and weaknesses of the study:**

The present study has a number of strengths making it a notable contribution to the present line of research. First, all participants were clinically diagnosed with Attention Deficit and Hyperactivity Disorder by clinical psychiatrist. Second, testing conditions were kept as consistent across the three days as possible: all tests were administered in the morning, and the same person was administering the test across all medication conditions. Third, for the titration part of the study conditions were blindly randomized and equally distributed across three days, which minimized experimenter bias and learning effect.

Besides valuable strengths, our study had considerable limitations. First, our conclusions about motor performance in children diagnosed with ADHD could have been statistically stronger if obtained data was compared to the data collected on typically developing children matched on age and IQ.

As a second important limitation of our study is a lack of a placebo condition in the titration design of our study. With the placebo –controlled design, our conclusion about treatment effect of MPH would be stronger. However, the main goal of the study was to examine the dose specific responses in cognitive and motor domain.

Third, in our study we did not examine the differences of dose-response curves according to ADHD subtypes since most participants (over 80%) of the titration part of the study met criteria for the combined subtype. Studies have indicated that there might

be a subtype-specific characteristic neurocognitive functioning (Tannock, 1998). These specific characteristics might also contribute to the specific dose–response characteristics.

Fourth, gender specific characteristics of the dose-response curve were not analyzed in the present study due to the small number of girls who participated in the study.

***Future directions***

A study comparing performance on motor tasks of children diagnosed with ADHD with children with no psychopathologies would contribute to the better understanding of the deficits specific to ADHD.

Effects of MPH on motor performance should be further assessed in a double-blind placebo controlled study in order to control for experimenter and participant biases.

A double-blind placebo controlled randomized study with a large sample is needed in order to further examine the effects of MPH on cognitive and motor functioning, specifically on the Motor-cognitive and Interference Control domains. A large sample will allow us to assess the contribution of the gender factor and to investigate characteristics specific to the clinical subtypes.

## CONCLUSION:

Consistent with our hypothesis, we observed differential dose-response of motor – cognitive action versus interference control domains to three different formulations of methylphenidate. We suggest that methylphenidate has a beneficial effect on the speed of the simple motor-cognitive action. The improvement is observed at low doses of MPH and increasing the dose from 0.3 to 0.8 mg/kg/day does not lead to further improvement. On the contrary, the effect of MPH on interference control is dose dependent and observed only at high doses (0.8 mg/kg/day). Furthermore, hyperactive symptoms such as excessive motor activation decline gradually as the dose of methylphenidate increases.

Our study provides preliminary indications that children diagnosed with ADHD do not perform on motor and verbal tasks as well as normally developing children of the same age.

Contrary to our original hypothesis that high dose of MPH will produce slowness in motor and cognitive domains, our study failed to find any evidence that MPH under 0.8 mg/kg/day leads to any decrease in speed of performance.

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*Appendix 1: Dose preparation table*

| Weight (kilograms) | | Low Dose (0.3 mg/kg) | | | Medium Dose (0.5 mg/kg) | | | High Dose (0.8 mg/kg) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| From | To | a.m. | p.m. | Total daily dose | a.m. | p.m. | Total daily dose | a.m. | p.m. | Total daily dose |
| 15.00 | 19.99 | 3.75 | 3.75 | 7.50 | 5.00 | 5.00 | 10.00 | 7.50 | 7.50 | 15.00 |
| 20.00 | 24.99 | 3.75 | 3.75 | 7.50 | 6.25 | 6.25 | 12.50 | 10.00 | 10.00 | 20.00 |
| 25.00 | 29.99 | 5.00 | 5.00 | 10.00 | 7.50 | 7.50 | 15.00 | 12.50 | 12.50 | 25.00 |
| 30.00 | 34.99 | 5.00 | 5.00 | 10.00 | 8.75 | 8.75 | 17.50 | 15.00 | 15.00 | 30.00 |
| 35.00 | 39.99 | 6.25 | 6.25 | 12.50 | 10.00 | 10.00 | 20.00 | 15.00 | 15.00 | 30.00 |
| 40.00 | 44.99 | 6.25 | 6.25 | 12.50 | 11.25 | 11.25 | 22.50 | 17.50 | 17.50 | 35.00 |
| 45.00 | 49.99 | 7.50 | 7.50 | 15.00 | 12.50 | 12.50 | 25.00 | 20.00 | 20.00 | 40.00 |
| 50.00 | 54.99 | 7.50 | 7.50 | 15.00 | 13.75 | 13.75 | 27.50 | 22.50 | 22.50 | 45.00 |
| 55.00 | 59.99 | 8.75 | 8.75 | 17.50 | 15.00 | 15.00 | 30.00 | 25.00 | 25.00 | 50.00 |
| 60.00 | ---- | 8.75 | 8.75 | 17.50 | 15.00 | 15.00 | 30.00 | 25.00 | 25.00 | 50.00 |

*Appendix 2: Consent form*

Information

Clinical and Pharmaco-genetic study of Attention Deficit with Hyperactivity Disorder (ADHD)

(Douglas Hospital Research Centre)

Drs Ridha Joober and Natalie Grizenko

Who is conducting this study?

This study is being conducted by a team of researchers including child psychiatrists (Drs Natalie Grizenko, Philippe Lageix), psychiatric geneticist (Dr Ridha Joober) and psychologist (Dr Valentin Mbekou) working in the field of attention deficit hyperactivity disorder (ADHD). The team is highly committed to exploring the causes and developing better treatments for ADHD. About 4-5% of youngsters in Canada and worldwide are affected with ADHD. The high frequency and the severe consequences of this disorder motivate our research.

Is ADHD inherited?

It has been known for a long time that ADHD tends to run in families. Also, ADHD may appear in families without a past history of this disorder. On the other hand, a child of two affected parents (that is, both parents having ADHD themselves) will not necessarily be affected. Recent scientific studies have confirmed these observations and show that genes are very important in predisposing an individual to ADHD. However, we still do not know <u>which</u> specific genes are involved in this disorder

What is the goal of this study?

There is strong evidence that one or several genes can lead to the behavioural changes observed in ADHD. Genes may also be involved in the way the disorder evolves (how severe it is and whether it responds to treatment medications or not). The purpose of this project is to identify genes that are involved in ADHD or that are involved in the way this

disorder responds to methylphenidate (Ritalin), the medication usually prescribed for treatment.

What are genes?

Genes are the basis of heredity between relatives. Each person inherits one set of genes from his/her father and a set from his/her mother. In our laboratory, we can identify and locate genes. The principal goal of our study is to find the genes inherited by children who have developed ADHD ("affected children"). For this purpose, we need the participation of affected children as well as their siblings (brothers and sisters) and parents.

Why are we looking for a different gene?

We believe that searching for a gene is one of the best strategies we have to find a cause for ADHD. Afterward, we can discover exactly what the gene does and what is different about it in people who have ADHD. We are hopeful this knowledge will help researchers to improve the treatment of this disorder by focusing their treatment on the specific problem.

What will be your role in this study?

Child with ADHD: Your child will be asked to have an interview with a doctor. He/she also will be asked to participate in neuropsychological testing that involves, performing computer tests where he/she will be asked to push a button when he/she sees specific signals, sorting cards, classifying figures, memorizing sequences of movements, drawing simple lines, choosing between different rewards and performing school type work. The child will also be asked to wear on his wrist a small watch-like device (actiwatch) that measures motor activity on two occasions to measure changes in activity levels during treatment.

In order to assess the quality of response to medication, each child who gives his/her assent (agrees) to participate will be given 0.5 mg/Kg of Ritalin per day divided in a twice a day dosing for one week and a sham medication (called "placebo" a capsule that looks exactly like the real medication but not containing Ritalin) for another week. Ritalin is the most used medication to treat ADHD and the dose of 0.5 mg/Kg is the usual

dose prescribed by physicians. The reason we give placebo and Ritalin for one week each is that the behaviour of the child may fluctuate from day to day. We therefore need a longer period to evaluate the changes under medication. The child, his/her parents and the treating physician will not know which week the child is receiving Ritalin or placebo. The child will be asked to put a small watch-like machine on his wrist (actiwatch). This watch is sensitive to movement and will measure the quality of his sleep. This watch will be put on the child's wrist when she/he goes to bed and take it off when she/he wakes up. During the two weeks, the child will be evaluated by his/her treating team, teacher(s) and parents.

Furthermore, in order to better determine the optimal dose for each child, three additional days will be included following the 2 week evaluation to observe the quality of response at 0.3, 0.5, and 0.8 mg/kg doses of Ritalin under additional testing conditions.

In order to study genes, we will need to take, on one occasion, a 40 cc (about 1 ounce or 40 ml) sample of blood. This small amount of blood is about twice the amount taken in a routine clinical blood test. Blood samples will be used to determine the frequency of some genes in children with ADHD in order to compare them to those of non-affected subjects (parents and siblings).

Parents: Parents will provide information about family history, complications which may have arisen during pregnancy and delivery, as well as the donation of a blood sample (40 ml) in order to carry out a comparison between their genes and those of their affected and unaffected children. Parents will be asked to complete a behavioural evaluation of their child on three occasions. Before the start of the medication trial, the parent will fill out a questionnaire regarding the presence and severity of sleep problems in his child. The parent will be asked to put and take off the motion sensitive watch on the wrist of his child during the two weeks of treatment. The parent will also complete a sleep log where he will note the time of turning off the light in the evening and turning the light on the next morning and document very briefly the quality of the sleep of their child. Parents will also be asked to complete a brief behavioural questionnaire and a diagnostic interview for each of their children.

Siblings: We will ask one non-affected sibling (the one who is closest in age and with the same gender whenever possible) to provide a blood sample. This blood sample will allow us to compare his/her genes with those of his/her affected sibling and his/her parents. Only siblings who assent to participate in this study will be included.

Withdrawal from the study

Parents can withdraw their children from this study at any time. The refusal to participate in the study will not affect the quality of care provided to the child.

Will participants benefit in any way from the study?

The advantages for your child in participating in this clinical and genetic study are that he/she will receive a comprehensive clinical and neuropsychological evaluation, free of charge. Results of this evaluation will be available to parents and the treating team of the child, if the parents agree. The results of the detailed clinical and neuropsychological evaluations may help his/her treating team and the school personnel in determining appropriate treatment for ADHD. The fact that the child will be treated one week with placebo and one other week with Ritalin will allow us and his/her treating team to see how the child responds to Ritalin under carefully monitored conditions and with a variety of specialized behavioural rating instruments and tests. The subsequent administration of several different doses of Ritalin will allow the treating team to fine-tune the dose of medication most beneficial to the child.

Your participation will help to increase knowledge about ADHD and may eventually lead to a better understanding of what causes ADHD, and may one day be useful in the treatment and prevention of ADHD.

Although it is not the primary purpose of this study, the genetic results may possibly lead to commercial applications. In this case, patients or their parents will not benefit from the commercial application resulting from having given blood.

Are there any risks to participating?

Our study includes the administration of a clinically relevant dosage of Ritalin, a medication that has been the treatment of choice for ADHD, in use for years. Sometimes the medication may induce side effects such as loss of appetite or nausea, difficulties with

sleep, upset stomach, tension, anxiety, dizziness, blurred vision or headaches. If these or other side effects occur, the treating physician could adjust the dose or, if necessary, stop the research study.

If your child is currently receiving Ritalin and is enrolled in the study, the fact that your child will not receive medication for a one week period is not expected to be associated with clinically significant discomfort. Indeed, it is rather good clinical practice to give medication holidays for children treated with Ritalin to reassess the need for medication.

The actiwatch, which measures motor activity during sleep, runs on battery and is insulated. It poses no risk.

For parents and siblings, there are no inconveniences except for having blood drawn, which can sometimes lead to bruising that disappears in a few days.

CONSENT FORM

Clinical and Pharmaco-genetic Study of ADHD

(For children in the day hospital program)

(McGill University)

Dr. R Joober & Dr. N Grizenko

I, _____, consent to have my

(please print)

children participate and participate myself in the clinical and genetic study on ADHD to be carried out by Drs Ridha Joober, Natalie Grizenko and associates of the Douglas Hospital Research Centre.

By signing this form:

1. I understand that the purpose of the study is to improve our knowledge about children with ADHD and to look for genes which may play a role in the cause of this disorder or in the way children with ADHD respond to medication. This investigation involves the study of children with ADHD, their parents and their siblings.

2. I confirm that my child and one of his/her non-affected siblings have agreed to participate in this study.

3. I agree to be interviewed by a health professional. During the interview I will be asked questions about my general health and whether I or members of my family have a history of mental illness, and, if so, the nature of the mental illness. The interview will last approximately 60-90 minutes. I will be interviewed about children's behaviour. The interview will last about 90-180 minutes. I will also be interviewed on events related to the pregnancy and birth of my child who is involved in this study and his/her siblings. This interview will also last 60 minutes. Finally, I will be asked to observe and assess the behaviour of my child on three occasions.

4. I agree that my child will undergo clinical and neuropsychological evaluations. All the evaluations are part of usual and good clinical practice for children with ADHD.

5. I agree that my child affected with ADHD will be treated for a period of one week with Ritalin at appropriate doses and one week with a sham medication (placebo) that looks

exactly like Ritalin but does not contain medication. My child, the treating physician, and myself will not know which week Ritalin or placebo are prescribed. I also agree that at the end of the two weeks of treatment, my child will receive 0.3, 0.5 and 1.0 mg/Kg of Ritalin on three different days. On each of these days, my child will receive neuropsychological and clinical evaluations that will allow the treating team to determine the optimal dose of Ritalin he/she may need.

6. I agree to document the quality of sleep of my child, and to complete a sleep schedule every day during the two weeks of the medication trial. This will be done with the help of a small watch-like machine which is sensitive to movement and which will measure the quality of sleep of my child. I will put this "watch" on my child's wrist when she/he goes to bed and take it off when she/he wakes up.

7. Before the start of the medication trial, I will fill out a questionnaire regarding the presence and severity of sleep problems in my child. My child will also be asked to rate his/her sleepiness.

8. I agree that my child affected with ADHD, one of his/her siblings not affected with ADHD and myself give a single 40 cc sample of blood (about 1 ounce, same as 40 ml) that will be drawn from an arm vein. This amount of blood is about twice the amount normally drawn for routine blood tests. Aside from minor discomfort and possibly some bruising, the procedure is quite safe. The blood sample will serve as a source of genetic material so that the investigators may look for genes that may be responsible for ADHD.

9. I have been informed and I agree that the results of clinical investigations and neuropsychological tests relevant for the clinical management of my child's condition will be available to the treating team. These tests and interviews are the following: Continuous Performance Test (CPT), Wisconsin Card Sorting Test (WCST), Self Ordered Pointing Test (SOPT), Tower of London, Wide Range Assessment of Memory and Learning (WRAML), Wide Range Achievement Test (WRAT-R), Delay Aversion Task, Wechsler Intelligence Scale for Children (WISC-III), interactive self report interview for children (Dominic), Child Behavioural Checklist, Conner's Global Index and the Diagnostic Interview Schedule for Children (DISC-IV) and Line-Drawing.

10. I have been informed that all information obtained during the study, except the tests listed in point 9, will be available only to researchers involved in the study and will remain confidential. To ensure confidentiality, information will be coded (i.e. names removed) and maintained in locked files. Genetic material will be identified by codes and stored in a secure facility accessible only to researchers involved in this study. This genetic material will be destroyed after 15 years of storage. If any scientific publication arises from the study my identity will not be revealed.

11. I have been informed that my child may benefit from a thorough clinical and neuropsychological evaluation. There is no charge for this evaluation. The results of the study may also help the treating team to adapt the treatment (including medication) that my child is receiving. Although it is not the primary purpose of this study, results from genetic testing may lead to commercial applications. In this case, I will not benefit from the commercial applications that would result, in part, from the blood and information I gave to the researchers.

12. I have the option, for myself and for my children, to withdraw from the study at any time without prejudice to any future care my relatives or I may require. In the case I want to withdraw, my genetic material will be destroyed.

13. I have been informed that if I have any questions about this research, I may contact by telephone either Dr Natalie Grizenko at (514) 761-6131 ext. 2113 or Dr. Ridha Joober at (514) 761-6131 ext. 2404 who will answer my questions. If I have any question about my rights as a patient, or as a research subject, I can phone the Douglas Hospital Ombudsman at (514) 762-3010 ext. 2255.

14. I have been given a copy of this information and consent form. The content of the information form has been explained to me to my satisfaction and my child has been explained the content of the information form in terms that are comprehensible to him/her.

_____ _____

Signature of Parent/Guardian Signature of Witness

Date:_____ Date:_____

_____ _____

Signature of Parent/Guardian Signature of investigator:

Date:_____ Date:_____

CONSENT FORM FOR FUTURE CONTACTS

Genetic and clinical study of ADHD

(McGill University)

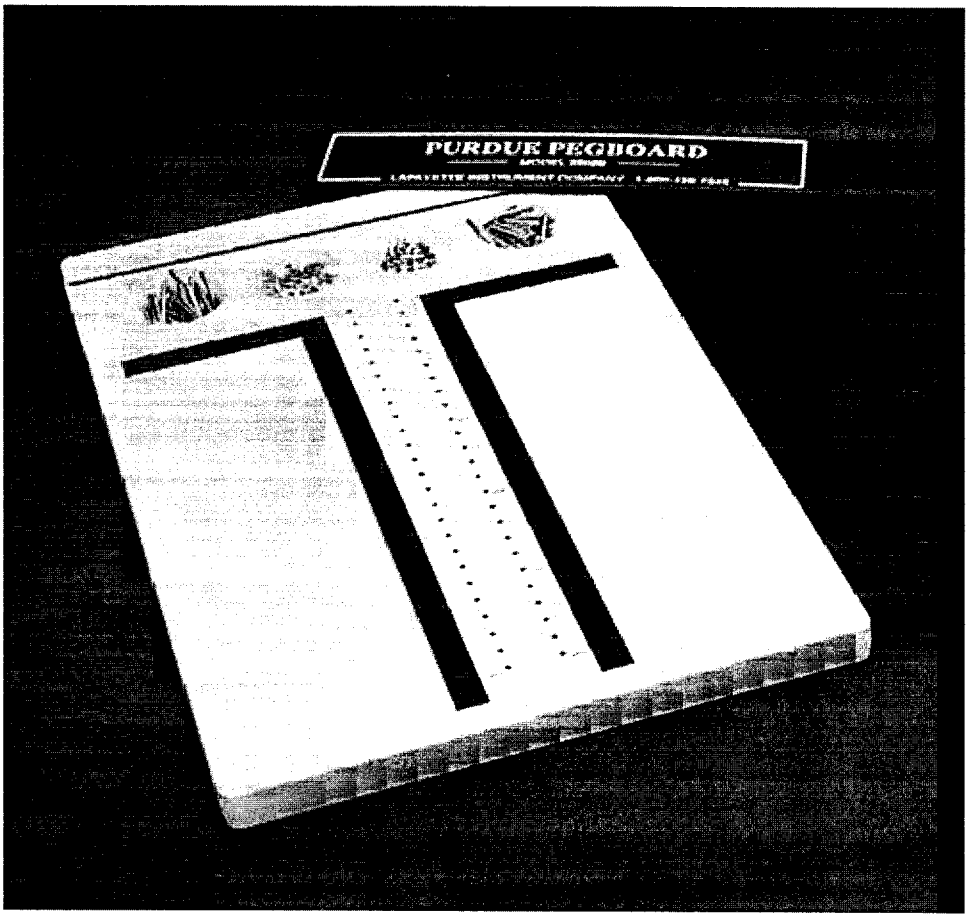
Dr. R Joober & Dr. N Grizenko

I, _____, give researchers conducting the clinical and genetic study on ADHD or their collaborators permission to contact me in the future: Check the box corresponding to your choice. You can check one or both choices

- ❑ To inform me of any relevant medical condition concerning my children or myself that they may discover while they are conducting their research.
- ❑ To inform me about the general findings of their research.

*Appendix 3: Purdue Pegboard Task*

(from **www.rehabzone.com/.../Purdue-Pegboard-Test.html**)



**Study Protocol # 99/22**

""Clinical and pharmaco-genetic study of Attention Deficit Hyperactivity Disorder (ADHD)"."

This letter concerns the protocol # 99/22 " Clinical and pharmaco-genetic study of Attention Deficit Hyperactivity Disorder (ADHD)" which was approved by the Douglas hospital ERB committee. The amendment involves three points.

**1. Determination of the optimal dose of methylphenidate for each child:**

Our current research protocol consists of a three day long titration assessment. The goal of the titration study is to assess behavioural and cognitive performance of children while receiving treatment with different doses of methylphenidate (MPH). . Evaluation consists of behavioural and neuropsychological tests, such as Self Ordered Pointing Test, Restricted Academic Situation Scale and WRAML – Finger Windows. Each of the three evaluation days are organized identically, apart from the dosage of MPH administered: pre-medication evaluation (roughly 30 minutes in duration), administration of one of the three dosage levels of MPH, and a post-medication evaluation 45 minutes after the pill is ingested.
Two additional tests will be added to the protocol and will be administered prior and post medication: Color and Word Test Children's Version (STROOP) (Golden C., Freshwater SM., Golden Z., 2003) and Purdue Pegboard (Tiffin J., 1948; Gardner R.A., Broman M., 1979). Administration of each test does not exceed 3 minutes; adding not more than a 15 minutes of evaluation time for each child. These tests will allow for the better assessment of the optimal dose and will give more detailed information about the cognitive and psychomotor performance of children.

**2. Decrease of the high dose used for the titration protocol**
Due to the previously reported by our subjects side effects, such as headaches, nervous movements and overall slowness, associated with the 1.0 mg/kg/day dose of MPH, we will decrease the dose to 0.8 mg/kg/day.

**3. Revisions of the information and consent forms**
Revisions of the information and consent forms have been made to accommodate the changes in our protocol discussed in the points 1 and 2.