UNIVERSIDADE FEDERAL DE MINAS GERAIS
**DANIELLE DE SOUZA COSTA**

# DIMENSÕES COMPORTAMENTAIS DO TRANSTORNO DE DÉFICIT DE ATENÇÃO/ HIPERATIVIDADE: INFLUÊNCIA PARENTAL E IMPACTO NO DESEMPENHO ESCOLAR

BELO HORIZONTE
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Dissertação de Mestrado apresentada ao Programa de Pós-Graduação em Medicina Molecular, Faculdade de Medicina, Universidade Federal de Minas Gerais, como requisito parcial à obtenção do título de Mestre em Medicina Molecular.

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**UNIVERSIDADE FEDERAL DE MINAS GERAIS**

**PROGRAMA DE PÓS-GRADUAÇÃO EM MEDICINA MOLECULAR**

# ATA DA DEFESA DA DISSERTAÇÃO DA ALUNA
# **DANIELLE DE SOUZA COSTA**

Realizou-se, no dia 04 de novembro de 2013, às 09:30 horas, Sala 526, Faculdade de Medicina, da Universidade Federal de Minas Gerais, a defesa de dissertação, intitulada *DIMENSÕES COMPORTAMENTAIS DO TRANSTORNO DE DÉFIT DE ATENÇÃO/HIPERATIVIDADE INFLUÊNCIA PARENTAL E IMPACTO NO DESEMPENHO ESCOLAR*, apresentada por DANIELLE DE SOUZA COSTA, número de registro 2012658924, graduada no curso de PSICOLOGIA, como requisito parcial para a obtenção do grau de Mestre em MEDICINA MOLECULAR, à seguinte Comissão Examinadora: Prof(a). Debora Marques de Miranda - Orientador (UFMG), Prof(a). Leandro Fernandes Malloy Diniz (ufmg), Prof(a). Marco Aurelio Romano Silva (UFMG), Prof(a). Breno Satler de Oliveira Diniz (UFMG).

A Comissão considerou a dissertação:

(X) Aprovada
( ) Aprovada condicionalmente, sujeita a alterações, conforme folha de modificações, anexa
( ) Reprovada

Finalizados os trabalhos, lavrei a presente ata que, lida e aprovada, vai assinada por mim e pelos membros da Comissão.
Belo Horizonte, 04 de novembro de 2013.

Prof(a). Debora Marques de Miranda
Doutora - UFMG

Prof(a). Leandro Fernandes Malloy Diniz
Doutor - UFMG

Prof(a). Marco Aurelio Romano Silva
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Doutor - UFMG

À minha mãe.

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**RESUMO**

COSTA, Danielle de Souza. **Dimensões comportamentais do Transtorno de Déficit de Atenção/Hiperatividade: influência parental e impacto no desempenho escolar.** Belo Horizonte, 2013. Dissertação (Mestrado em Medicina Molecular)- Faculdade de Medicina, Universidade Federal de Minas Gerais, 2013.

O Transtorno de Déficit de Atenção/Hiperatividade (TDAH) está entre os transtornos psiquiátricos mais frequentes e mais bem validados em neuropsiquiatria. Contudo, sua apresentação clínica é bastante heterogênea com marcada instabilidade no curso dos sintomas. Os aspectos peculiares às dimensões comportamentais do TDAH (desatenção e hiperatividade-impulsividade) estão intimamente relacionados à sua heterogeneidade fenotípica. Este estudo buscou investigar 1) se medidas simples de identificação do nível de sintomas nos pais teriam um poder preditivo na identificação dos sintomas em seus filhos e como isso ocorre no nível fenotípico; 2) como a capacidade cognitiva global (inteligência) influencia a associação entre os sintomas de TDAH e desempenho acadêmico. Verificou-se que os sintomas de TDAH maternos respondem por cerca de ¼ da variância dos sintomas de TDAH em seus filhos. Esta forte influência se dá de modo predominante pela dimensão hiperativo-impulsiva materna que parece ser responsável essencialmente pelos fatores fenotípicos compartilhados entre as dimensões desatenta e hiperativo-impulsiva dos estudantes. Adicionalmente, foi observado que a influência dos sintomas maternos sobre os sintomas de hiperatividade-impulsividade pode ser em alguma medida indireta, sendo primariamente exercida sobre os sintomas de desatenção e secundariamente sobre os de hiperatividade-impulsividade. Os sintomas de desatenção também foram centrais em relação ao desempenho escolar: maiores prejuízos cognitivos globais poderiam levar a um nível maior de desatenção o que, por sua vez, levaria a um pior desempenho acadêmico. Embora os sintomas de hiperatividade-impulsividade não tenham apresentado associação significativa com a inteligência geral, em alguns casos, quando presentes tornaram ainda mais intensa a relação entre os sintomas de desatenção com o desempenho escolar.

**Palavras-Chave:** Comportamento parental, Desatenção, Desempenho escolar, Etiologia, Funcionalidade, Hiperatividade-impulsividade, Inteligência Geral, TDAH.

**ABSTRACT**

COSTA, Danielle de Souza. Behavioral dimensions of Attention Deficit/Hyperactivity Disorder: parent's ADHD behavior influence and children's ADHD impact on academic performance. *[Dimensões comportamentais do Transtorno de Déficit de Atenção/ Hiperatividade: influência parental e impacto no desempenho escolar]*. Belo Horizonte, Brazil, 2013. Dissertation (Masters in Molecular Medicine) - Faculdade de Medicina, Universidade Federal de Minas Gerais, 2013.

Attention Deficit/Hyperactivity Disorder (ADHD) is among the most common and valid psychiatric disorders. However, ADHD symptoms course remains unclear due to its very heterogeneous clinical presentation. Differences between ADHD behavioral dimensions (i.e., inattention and hyperactivity-impulsivity) may account for ADHD phenotypic heterogeneity and to understand how they are related at the behavioral level is of utmost importance. This study investigated 1) how mothers' ADHD symptoms influence children's inattentive and hyperactive-impulsive symptoms, and 2) how ADHD dimensions are related to intelligence and academic performance. First, we found that maternal hyperactive-impulsive symptoms were the main influence on the shared variance between children's inattention and hyperactivity-impulsivity. Notwithstanding, some of the maternal symptoms' influence on children's hyperactivity-impulsivity was accounted for by children's inattentive symptoms. Second, the results showed that ADHD inattention mediates the influence of general intelligence on academic performance. Even though hyperactivity-impulsivity was not related to intelligence, it was a moderator of inattentive symptoms' impact on academic performance.

**Keywords:** Parental behavior, Inattention, Academic performance, Etiology, Functionality, Hyperactivity-impulsivity, General intelligence, ADHD.

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## LISTA DE ABREVIATURAS E SIGLAS

| | |
|---|---|
| ABEP | Brazilian Research Enterprises Association |
| ADHD | Attention-deficit/hyperactivity disorder |
| ADHD-C | ADHD Combined Subtype |
| ADHD-H | ADHD Hyperactive Subtype |
| ADHD-I | ADHD Inattentive Subtype |
| APA | American Psychological Association |
| ASRS | Adult Self-Report Scale- version 1.1 for adult evaluation of ADHD symptoms |
| CCEB | Brazilian Criterion of Economic Classification |
| DSM-IV | Diagnostic and Statistical Manual of Mental Disorders |
| GEE | Generalized Estimated Equations |
| ID | Intellectual Disability |
| INCT-MM | Instituto Nacional de Ciência e Tecnologia em Medicina Molecular |
| K-SADS-PL | Kiddie-Sads-Present and Lifetime Version |
| LIN | Laboratório de Investigações Neuropsicológicas |
| MTA SNAP-IV | Swanson, Nolan, and Pelham– version IV for evaluation of ADHD symptoms |
| Raven's CPM | Raven's Colored Progressive Matrices |
| SAT | School Achievement Test |
| SES | Socioeconomic status |
| SPSS | Statistical Package for Social Sciences |
| TA | Transtornos de aprendizagem |
| TD | Typically developing students |
| TDAH | Transtorno de Déficit de Atenção/ Hiperatividade |

**SUMÁRIO**

## 1 - INTRODUÇÃO

O Transtorno de Déficit de Atenção/ Hiperatividade (TDAH) pode ser descrito como um transtorno crônico e estável ao longo do desenvolvimento, marcado por um padrão persistente de desatenção e/ou hiperatividade-impulsividade.[1-3] O TDAH é geralmente um transtorno comportamental bastante evidente não só na idade escolar, mas também na pré-escola, adolescência e adultez. Sua prevalência depende de três fatores principais: a população amostrada, o método de avaliação e o critério diagnóstico,[4] mas geralmente é elevada com a maior parte dos estudos reportando frequências entre 5% a 10% da população.[5]

A pesquisa sobre a etiologia do TDAH traz informações importantes sobre diferenças de hereditariedade, morfológicas e funcionais. Prejuízos funcionais são documentados em múltiplos domínios o que sugere que o TDAH é neuropsicologicamente heterogêneo. Os domínios gerais consistentemente implicados no TDAH são: 1) atenção, 2) funções executivas “frias”, 3) regulação de estado, 4) motivação e 5) processamento de informação temporal.[6] Considerando todos esses domínios conjuntamente, entre 50-70% dos sujeitos com TDAH podem apresentar algum tipo de prejuízo neuropsicológico. Embora estejam associadas, essas funções possuem vias neurobiológicas relativamente independentes: 1) via fronto-estriatal dorsal, envolvida no controle cognitivo (funções executivas “frias”); 2) via fronto-estriatal ventral, envolvida no processamento de recompensas (sensibilidade ao reforço e aversão à espera pela recompensa); e 3) via fronto-cerebelar, relacionada ao processamento de tempo. Uma quarta via poderia estar mais relacionada à regulação de estado (essencialmente aos aspectos de ‘vigilância’). [7] Um atraso no desenvolvimento da espessura cortical, mais pronunciado nos lobos frontais, também é reportado em portadores do transtorno.[8] A herdabilidade estimada do TDAH varia de 60% a 90% e o sistema dopaminérgico parece especialmente implicado. [9,10]

Apesar desse corpo de evidências ainda é surpreendentemente comum ao público leigo representações de portadores de TDAH como crianças sem limites, desenfreadas, desordeiras, desobedientes; na adolescência podem ser vistos como “drogados”, baderneiros.[4] Não há dúvida de que a atenção pública está voltada há um tempo para o TDAH, embora sua visão seja geralmente negativa o que tem trazido impacto importante para os portadores, inclusive por parte de profissionais da saúde e no âmbito público, que negligenciam as necessidades ainda mais evidentes de tratamento do transtorno, principalmente na adultez.[4] Por outro lado, dificuldades intrínsecas ao campo de estudo

ainda contribuem como barreiras para o desenvolvimento de políticas públicas voltadas para a identificação precoce e delineamento de planos de intervenção. Embora seja um dos transtornos do desenvolvimento mais estudados e bem validados em neuropsiquiatria, a elevada heterogeneidade do TDAH em termos de curso dos sintomas e desfechos funcionais continua sendo um desafio para o desenvolvimento de modelos etiológicos e prognósticos mais estáveis e preditivos.[3,11,12] A inconsistência dos resultados no estudo do TDAH pode decorrer, ao menos em parte, de sua heterogeneidade e complexidade clínica.[13]

Os modelos que definem o TDAH em subgrupos a partir de diferenças quantitativas, considerando as dimensões comportamentais do TDAH dentro de um *continuum* de gravidade, têm melhores evidências de validade.[3] Lahey e Willcutt (2010) argumentam que a melhor forma de definir o TDAH seria como um transtorno único (sem subtipos) especificado por modificadores dimensionais. Os autores propõem faixas sintomáticas cuja severidade seria determinada pela quantidade de sintomas correntes (p.ex., 0-2 leve/baixo; 3-5 moderado/subclínico; ≥6 alto/grave).[12] Mais que o diagnóstico categórico, entender o comportamento quantitativo das dimensões comportamentais do TDAH é fundamental para o alcance de modelos mais estáveis. Os sintomas de desatenção têm menor declínio ao longo do desenvolvimento, estão mais relacionados a problemas escolares, baixa popularidade entre os pares e a sintomas internalizantes.[3] A dimensão hiperativa-impulsiva, por outro lado, sofre declínio de sintomas com o aumento da idade, está mais relacionada à rejeição pelos pares, acidentes não intencionais, mau relacionamento com pais e professores e problemas de conduta geral.[3] Esses aspectos peculiares às dimensões comportamentais do TDAH estão intimamente relacionados à sua heterogeneidade fenotípica. A investigação dos fatores preditivos de sua expressão no nível comportamental permitiria conclusões mais precisas em relação à variabilidade do TDAH, acrescentando informações relevantes para pautar iniciativas relacionadas ao estudo de sua etiologia, procedimentos diagnóstico, prognóstico e de intervenção mais específicos.

Outra forma de aumentar o poder preditivo sobre o curso do TDAH seria avaliar como suas dimensões comportamentais estão associadas a sofrimento e prejuízos funcionais. No TDAH, quanto mais sintomas do transtorno, maior a probabilidade de prejuízos futuros.[3] O baixo desempenho escolar, por exemplo, é um dos desfechos mais usuais do transtorno. O TDAH frequentemente co-ocorre com transtornos de aprendizagem (TA) e vice-versa (taxa média de comorbidade igual a 45%).[14] Em geral, o desempenho de indivíduos com TDAH é moderadamente inferior ao dos pares com desenvolvimento típico, sendo o prejuízo maior para crianças, porém permanecendo até a

adultez.[15] Mesmo sujeitos com TDAH sem diagnóstico comórbido de TA apresentam mais dificuldades escolares, contudo tanto o TDAH quanto os TA são mais graves quando co-ocorrem.[16]

A associação entre os sintomas de TDAH e o desempenho escolar é influenciada tanto por fatores genéticos quanto ambientais compartilhados envolvendo prejuízos cognitivos significativos.[17-20] De fato, um dos principais modelos neuropsicológicos do TDAH sugere que seus sintomas surgem de um déficit primário nas funções executivas (processos neurocognitivos que permitem e mantêm a capacidade de resolução de problemas dirigida a metas específicas). [21,22] Paradigmas de avaliação da atenção que envolvem componentes de funções executivas (processos atencionais controlados) também são importantes preditores do desempenho acadêmico.[23] Outra função cognitiva geral relacionada tanto ao TDAH quanto aos TA é a inteligência fluida. Numa perspectiva de desenvolvimento, o construto inteligência pode ser descrito como um índice de funcionamento cognitivo global resultante de influências multifatoriais.[24] Do ponto de vista psicométrico, ele é geralmente dividido em dois construtos principais interrelacionados: inteligência fluida e cristalizada.[25,26] A inteligência cristalizada é fruto do conhecimento semântico adquirido com as experiências vividas, já a inteligência fluida reflete um conjunto de habilidades de raciocínio que opera em diversos contextos, principalmente no manejo de situações novas.[27] Embora essas habilidades cognitivas gerais estejam fortemente relacionadas tanto aos sintomas do TDAH quanto ao desempenho acadêmico, ainda não está claro como esses três aspectos se relacionam no nível fenotípico.

Considerando que o esclarecimento de questões importantes no nível comportamental tem um potencial elevado para uma aplicação mais direta no nível público, o presente trabalho buscou investigar 1) se as dimensões comportamentais do TDAH são fortemente herdadas, medidas simples de identificação do nível de sintomas nos pais teriam um poder preditivo na identificação dos sintomas em seus filhos? Se sim, como isso ocorre no nível fenotípico; 2) a utilização de instrumentos de triagem cognitiva pode ser útil na identificação de grupos mais suscetíveis a um desempenho escolar prejudicado? Ou seja, a capacidade cognitiva global influencia a associação entre os sintomas de TDAH e desempenho acadêmico? Esclarecer quais e como os comportamentos dos pais podem prever os sintomas de TDAH nas crianças, bem como identificar como esses sintomas estão relacionados a problemas funcionais como o desempenho escolar é fundamental para aumentar a consistência das investigações relacionadas à etiologia e ao curso do TDAH, bem como de intervenções precoces e eficazes.

*1.1 Estrutura da dissertação*

A presente dissertação foi organizada em 2 artigos. O primeiro artigo intitulado '*The influence of maternal behavior on ADHD traits in children: inattention as a mediator factor?*' traz um modelo de mediação da influência dos sintomas maternos sobre a manifestação das dimensões comportamentais do TDAH em seus filhos. Esse artigo será submetido ao periódico *Journal of Attention Disorders* em que são publicadas pesquisas sobre diagnóstico, comorbidades, além de funcionamento neuropsicológico, psicofarmacológico e psicossocial da atenção e outras funções relacionadas. O artigo foi redigido em inglês e segue as demais normas de publicação da revista que são as descritas no manual da *American Psychological Association* (APA, 2001).

O segundo artigo da dissertação intitulado '*ADHD inattentive symptoms mediate the relationship between Intelligence and Academic performance in children aged 6–14'* propõe um modelo sobre a relação entre inteligência fluida e os sintomas de TDAH e sua influência no desempenho escolar. O artigo 2 foi submetido à *Revista Brasileira de Psiquiatria.* A revista contempla estudos relacionados à psiquiatria com ênfase na saúde pública, epidemiologia clínica e ciências básicas, além de outros tópicos relevantes para o campo da psiquiatria. A formatação do artigo segue as regras peculiares à revista o que inclui a redação do mesmo em inglês.

## 2 - OBJETIVOS

### 2.1 Objetivo geral

Investigar como os sintomas parentais influenciam as dimensões comportamentais do Transtorno de Déficit de Atenção/Hiperatividade, além de estudar como essas dimensões comportamentais se relacionam com prejuízos no nível cognitivo trazendo impacto ao desempenho escolar.

### 2.2 Objetivos específicos

- Verificar como os sintomas de desatenção e de hiperatividade-impulsividade maternos influenciam esses sintomas em seus filhos, numa amostra de escolares do Ensino Fundamental;

- Investigar como os sintomas de desatenção e de hiperatividade-impulsividade se relacionam no nível comportamental a partir de modelos de mediação estatísticos;

- Estudar a partir de medidas objetivas de inteligência e de desempenho escolar (escrita e matemática) qual o papel dos sintomas de TDAH na relação entre o nível de funcionamento cognitivo geral e problemas acadêmicos;

- Investigar o papel de características sociodemográficas como idade, gênero e nível socioeconômico nos modelos explicativos que envolvem a análise das dimensões comportamentais do TDAH.

## 3- The Influence of Maternal Behavior on ADHD Traits in Children: Inattention as a Mediator Factor?

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**Abstract**

**Objective:** To evaluate, through a series of mediation analysis, how ADHD dimensions in mothers influence the manifestation of the same ADHD dimensions in their offspring. **Method:** A total of 117 students from 6-to-16 years without clinical diagnosis of psychiatric disorders and 117 mothers had their ADHD symptoms measured by structured questionnaires. **Results:** Data suggested that the influence of maternal symptoms on children's symptoms was mainly exerted by the hyperactivity-impulsivity dimension. That influence was primary accounted for by the shared variance within children's ADHD inattention and hyperactivity-impulsivity (ADHD "general factor"). Additionally, children's inattentive variance explained some of the impact of maternal hyperactivity-impulsivity on their offspring hyperactive-impulsive symptoms. **Conclusion:** Our findings help us to better understand how the mother's ADHD behavior influences the manifestation of ADHD dimensions in their offspring. That comprehension is of utmost importance to develop strategies for early diagnosis and intervention to prevent the deleterious effects of ADHD symptoms on child development.

**Keywords**

Attention-deficit/hyperactivity disorder, Hyperactivity-impulsivity, Inattention, Mediation, Parental influence

**3.1 INTRODUCTION**

Attention-deficit/hyperactivity disorder (ADHD) is characterized by two main symptomatic dimensions: inattention and hyperactivity-impulsivity (Doyle et al., 2005). It is a highly heritable condition, and 25% to 30% of children with ADHD have at least one parent affected with the disorder (Faraone, & Biederman, 1997). An even higher percentage of children with ADHD have parents with subsyndromal manifestation of ADHD, but how parent ADHD symptomatic dimensions influence their offspring symptoms is largely unknown.

Children behavior frequently is described by their parents and mainly by the mother in several investigations (Burt, McGue, Krueger, & Iacono, 2005). Maternal reports usually suggest important genetic effects on ADHD variance and, on the other hand, absence of shared environmental influences (Burt, 2009; Burt, 2010; Burt, Larsson, Lichtenstein, & Klump, 2012; Burt, McGue, Krueger, & Iacono, 2005; Eaves et al. 2000; Simonoff. et al., 1998). The genetic component is largely observed when assessed using questionnaires (Burt, 2009). However, despite common genetic influences explain most of the phenotypic covariance between inattentive and hyperactive-impulsive dimensions across a range of severity (Gillis, Gilger, Pennington, & DeFries, 1992; Levy, Hay, McStephen, Wood, & Waldman, 1997; Larsson et al. 2006; Larsson et al., 2013; Sherman, Iacono, & McGue, 1997; Schultz et al., 2006) these two dimensions seem to be differentially heritable (Willcutt et al., 2000). Inattention symptoms are highly heritable regardless of the level of hyperactive-impulsive symptoms. In contrast, the heritability of hyperactivity-impulsivity increases as a linear function of the number of inattentive symptoms (Willcutt et al., 2000). It suggests that inattentive symptoms may moderate the genetic etiology of hyperactivity-impulsivity. Additionally, Willcutt et al. (2012) analysed 546 studies on ADHD and at different neurobiological, behavioral, and functional levels their data indicates that the ADHD inattentive dimension may account for by most of the underlying mechanisms influences on ADHD hyperactive-impulsive symptoms. Therefore, ADHD inattention appears to both moderate and mediate underlying influences on ADHD hyperactivity-impulsivity. Thus, it is reasonable to expect that parental ADHD symptoms may primarily influence their offspring inattentive symptoms. However, we must consider two things.

First, although additive genetics influences are large for both ADHD dimensions, they are even higher for hyperactivity-impulsivity while non-additive genetic effects are higher for inattention. Also, despite small effect sizes, non-shared environmental influences may be larger for inattention than for hyperactivity-impulsivity (Nikolas, & Burt, 2010). When additive genetic influence operates, we would

observe similarities between parents and children, but non-additive genetic effects and non-shared environmental influences usually do not result in parent-child similarity. Therefore, parental hyperactivity-impulsivity is probably a stronger predictor of children ADHD symptom domains. Second, at the behavioral level most of the ADHD symptoms might be clustered under a general dimension across several conditions. This general ADHD factor account for a great amount of the inattentive dimension (35-48%) and the hyperactive-impulsive dimension (23-54%) (Normand, Flora, Toplak, & Tannock, 2012; Toplak et al., 2009; Toplak et al., 2012). It is thus theoretically possible that parental ADHD symptoms mainly influence this shared variance between inattentive and hyperactive-impulsive symptoms named as general factor.

Since the influence of parent ADHD symptom dimensions on their offspring inattentive or hyperactive-impulsive domains remains fairly unclear we aimed to test how this may occur in a school population sample. We hypothesized that parent hyperactive-impulsive domain is a stronger predictor of both children ADHD symptom dimensions; but we are also expecting that parental behavior will primarily influence children inattentive domain, which in turn will exert an influence on their own hyperactive-impulsive symptoms. Intervenient factors on ADHD symptoms development, such as children age and gender and family socioeconomic status also will be tested as possible modifiers of this hypothetical mediation model. As long as genetic influences may increase with age (Lyons et al. 1995; McGue et al. 1993) parent influences would be more observable among older children. ADHD etiology might differ between genders with highly genetic loadings in girls (Goos et al., 2007; Hawi et al., 2005; Rhee et al., 1999). Also, low socioeconomic status is associated with increased rates of ADHD (Biederman et al., 1995, 2002; Pineda et al.,1999).

The understanding of how parent's ADHD symptoms influence children's symptoms is of utmost importance to develop strategies for early diagnosis and intervention to prevent the deleterious effects of ADHD symptoms on child development.

## 3.2 METHODS

### *3.2.1 Participants*

All families (n=598) of a public elementary school (i.e., from first to ninth grade) from Belo Horizonte, Brazil, were invited to participate in a screening survey for ADHD symptoms. One hundred thirty-nine families consented to participate in the study and answered questionnaires about ADHD-related symptomatology and socioeconomic status (SES). Seventeen families were excluded for not giving information by at least one parent. Given the low number of paternal questionnaires returned

(n=52) only maternal responses were included as a parent ADHD-related measure. Another 5 families were excluded because children were previously diagnosed with a psychiatric disorder (3 children were being treated with antidepressant, one with antipsychotic, and one with psychostimulant). Final sample was composed by 117 students without clinical diagnosis of psychiatric or developmental disorders and their mothers. This sample was representative of the public elementary school from the city in which the study as carried out with a 3.54 confidence interval. It is important to note that 6% (n=7) of students scored on parent short version of the Swanson, Nolan, and Pelham– version IV (MTA SNAP-IV) above cutoff scores that increase the probability of an ADHD diagnosis (Bussing et al., 2008). The student ages ranged from 6-to-16 years. All mothers (ages 23 to 52) declared to be biologically related to the participating students. This study was approved by the local Ethics Committee Board (ETIC 567/11).

*3.2.2 Measures*

*3.2.2.1 Socioeconomic status*

Socioeconomic status was assessed using the Brazilian Criterion of Economic Classification (CCEB) according to the Brazilian Research Enterprises Association (ABEP, 2008). The CCEB estimates the power to purchase of families living in urban areas. It includes 9 items that assess the available resources at home and 1 item that assesses the education level of the householder, resulting in a scale ranging from 0 to 46 points. Families categorized into high class (23 to 46 points) have a monthly income ranging from U$1300 to U$4712, and families categorized into low class (0 to 22 points) has a monthly income ranging from U$380 to U$825. The families on this study presented scores varying from 12 to 42 (M=24.5, SD=6.5). Fifty-six percent of participants are in the high SES and 44% in the low range of Brazilian SES. Since CCEB mainly measures income level, we also included mother education to evaluate SES. Mother education ranged from 7-to-16 years ($M$=12.13, SD=2.54) and was significantly correlated to CCEB ($r$(89)=0.36, $p$=0.001). We did not include children education because in our school-based sample grade level seemed to reflect children age ($r$(109)=0.96, $p$<0.001).

*3.2.2.2 ADHD-related symptomatology*

Structured questionnaires based on the Diagnostic and Statistical Manual of Mental Disorders [4th ed., DSM-IV; APA, 1994] symptoms of ADHD were sent to the students' homes. Parents

completed the Brazilian version of the Swanson, Nolan, and Pelham– version IV (SNAP-IV; Mattos et al., 2006a) for evaluation of ADHD symptoms in their children and the Brazilian version of Adult Self-Report Scale- version 1.1 (ASRS; Mattos et al., 2006b) for assessment of ADHD in themselves. The SNAP-IV is an 18-item measure, each of which is rated on a 4-point Likert scale (0–3 point anchors), with items summed to form a total score. The ASRS is an adult version of ADHD screening, also an 18-item measure, yet rated on a 5-point Likert scale (0–4 point anchors). The sum of the first 9 items of those scales describes the total level of inattentive behaviors and the sum of the last 9 items reflects hyperactive-impulsive behaviors. The sum of all 18 items represents the overall ADHD-related symptoms. Children questionnaires were mainly responded by mothers (89%) and no mother or father filled out more than one questionnaire. Children scores reported by fathers (n=13) were not excluded to increase statistical power. Children ADHD data from each student was only obtained by maternal or paternal report and never by both.

#### *3.2.2.3 Data Analysis*

SNAP-IV and ASRS data were transformed into z-scores to depict the measures on the same scale. The z-scores were used in all analysis except for sample characterization. The data was normally distributed according to the Kolmogorov-Smirnov test ($p > 0.05$).

In a simple mediation model, all variables must be related (Baron, & Kenny, 1986; Iacobucci, Saldanha, & Deng, 2007). Thus, firstly we showed the direct effects of all candidate variables. Maternal symptoms were tested as predictors of children symptoms in generalized estimated equations (GEE) with a linear regression model, robust estimators, and exchangeable structure for working correlation matrices. Family number was used as subject effect to account for clustered data (familial dependency within the data set). Separate analyses were run for each of the dependent variables.

To investigate whether it was possible to infer the direction of the relationship between children ADHD symptoms dimensions in our sample, independent linear regression analysis was performed. The standardized sum of all 18 SNAP-IV items was inserted as dependent variable. Inattentive z-scores and hyperactive-impulsive z-scores were inserted as independent variables, separately. Then, a stepwise linear regression analysis was conducted with both independent variables together to show the change in contribution for the overall symptoms. In regression analysis when we observe a significant decrease of a direct effect when a second independent variable is

inserted in the regression model this is an indication of that second predictor accounts for the relation between the first predictor and the dependent variable (Baron & Kenny, 1986). This is just a step by step of simple mediation analysis. Besides significantly decreased the total effect of the predictor variable on the outcome variable, a mediator should not be caused by the outcome variable (Preacher, & Hayes, 2004). However, at this point of knowledge it is difficult to predict a clearly hierarchical relationship between inattention and hyperactivity-impulsivity in ADHD symptomatology. Supposing as we hypothesized that inattentive symptoms precede hyperactive-impulsive symptoms in our sample, in the stepwise linear regression model the predictive power of inattention on overall ADHD symptoms will remain almost the same, whereas the predictive power of hyperactivity-impulsivity will decrease since inattention may be closely related to general factors shared between overall ADHD symptoms. If all these assumptions were confirmed, we planned to conduct a GEE with the same previous parameters using children's hyperactive-impulsive symptoms as the outcome variable and maternal symptoms and children's inattentive symptoms together as predictors. We expected that the influence of maternal behavior on children hyperactive-impulsive symptoms would be accounted for by children inattention. Mediation effects were computed using a multiple mediation analysis macro for SPSS developed by Preacher, and Hayes (2004).

To investigate whether the strength of the simple mediation model of maternal influence on children ADHD symptoms change in face of contextual variables, children age and gender, and family socioeconomic factors were evaluated in moderated-mediation analysis. To provide a better discussion on this topic, avoiding Type II error due to lack of statistical power for the moderated-mediation analysis, we also reported the simple mediation effect for each tested moderator with a 5000 bootstrap method. We performed this subsampling in our data according to their categorical classification and run separated mediation analysis for each category (e.g., first only for children from male group than from female group). Dimensional variables as age were turned on three categorical classifications: the first representing values 1SD below the mean, the second representing values 1SD within mean, and the last one accounting for values 1SD above the mean (Hayes, 2012). Moderated-mediation effects were performed using a computational tool for observed variable mediation, moderation, and conditional process modeling for SPSS developed by Hayes (2012). The Statistical Package for Social Sciences (SPSS) software, version 20.0, was used for statistical analysis (IBM Corporation, Armonk, NY, USA).

**3.3 RESULTS**

Male children showed higher inattention scores compared to female participants ($t(116) = 2.0$, $p<0.05$), but there were no differences for hyperactive-impulsive scores. We also did not find significant correlations between scores on SNAP-IV and age, grade or SES. On the other hand, maternal inattention was significantly correlated to SES ($r(115)=0.31$, p<0,001). Table I summarize sample characteristics and Pearson correlations between ADHD-related symptoms and possible conditional variables are shown in table II.

**Table I.** Sample Characteristics

| | **Mothers** | **Children** | | |
|---|---|---|---|---|
| | (n=117) | Male (n=62) | Female (n=55) | Overall (n=117) |
| Age (years) *M(SD)* | 37.6 (6.1) | 9.16 (2.27) | 9.55 (2.69) | 9.3 (2.5) |
| Education (years) *M(SD)* | 12.13 (2.54) | 3.79 (2.08) | 4.30 (2.72) | 4.02 (2.39) |
| High SES *N*(%) | 65 (56%) | 39 (63%) | 26 (47%) | 65 (56%) |
| ADHD symptoms[a] *M(SD)* | | | | |
| *Inattention* | 10.0 (5.3) | 8.56 (5.26) | 6.60 (5.32) | 7.6 (5.4) |
| *Hyperactivity-impulsivity* | 10.8 (5.6) | 6.05 (4.42) | 5.76 (4.69) | 5.9 (4.5) |

[a] The table show descriptive statistics of raw scores. The SNAP-IV was used to measure children ADHD-related behavior, and the ASRS to measure maternal ADHD-related behavior.

**Table II.** General correlations of ADHD symptom dimensions with Age, Education, and Family Income Level

| | **Age (years)** | **Education (years)** | **SES** |
|---|---|---|---|
| Children Inattention | 0.06 | 0.10 | -0.08 |
| Children Hyperactivity-impulsivity | 0.11 | 0.07 | -0.01 |
| Maternal Inattention | 0.05 | 0.09 | 0.31** |
| Maternal Hyperactivity-impulsivity | -0.04 | -0.06 | 0.08 |

SES= Socieconomic Status measured by a Brazilian instrument of family income level

**. Correlation is significant at the 0.001 level (2-tailed).

Direct effects of maternal symptoms on children's symptoms are summarized in table III. GEE model showed that maternal inattentive symptoms significantly predicted offspring inattentive scores, but not children hyperactivity-impulsivity. In turn, maternal hyperactive-impulsive scores significantly predicted scores on both offspring ADHD-related domains. It was interesting to note that the direct effect on children inattention was a little higher for maternal hyperactivity-impulsivity than for maternal inattention. In fact, when both maternal ADHD symptoms dimensions were inserted together in GEE

model maternal inattentive symptoms influence on children's inattentive symptoms was reduced to a non-significant level ($\beta$= 0.19, $p$<0.02 *vs* $\beta$= 0.11, $p$<0.22) while maternal hyperactive-impulsive symptoms remained a significant predictor of children inattention ($\beta$= 0.26, $p$<0.003 *vs* $\beta$= 0.22, $p$<0.02). These overall results suggest that, despite significant shared variance between maternal symptoms dimensions ($R^2$=0.13, $F$(1,115)=17.03, $p$ <0.001), maternal hyperactive-impulsive dimension was the main predictor of both offspring ADHD behavioral dimensions. Thereon maternal hyperactivity-impulsivity was the only maternal dimension eligible for a simple mediation model with children ADHD symptoms dimensions.

**Table III.** Direct effects of maternal ADHD symptom domains on children ADHD symptoms

| **Predictor** | **Outcome** | ***B*** | **95%CI** | ***p-Value*** |
|---|---|---|---|---|
| Mother INATT | Children INATT* | 0.19 | 0.03-0.34 | 0.02 |
| | Children HYP-IMP | 0.06 | -0.11-0.22 | 0.51 |
| Mother HYP-IMP | Children INATT** | 0.26 | 0.09-0.43 | 0.003 |
| | Children HYP-IMP* | 0.23 | 0.04-0.43 | 0.02 |

INATT= Inattentive symptoms; HYP-IMP= Hyperactive-impulsive symptoms

*. Correlation is significant at the 0.05 level (2-tailed); **. Correlation is significant at the 0.01 level (2-tailed).

To clarify the relationship of inattentive and hyperactive-impulsive symptoms with overall ADHD symptoms in our sample we observed how each dimension influenced ADHD symptoms separately and together which was done only for children. Inattention and hyperactivity-impulsivity were stronger predictors of overall ADHD symptoms separately ($\beta$= 0.90, $t$(115)=22.44, $p$<0.001, and $\beta$= 0.86, $t$(115)=18.10, $p$<0.001, respectively). When analyzed together in a stepwise linear regression model both inattentive symptoms ($\beta$= 0.90, $p$<0.001 *vs* $\beta$= 0.61, $p$<0.001) and hyperactive-impulsive symptoms ($\beta$=0.86, $p$<0.001 *vs* $\beta$= 0.52, $p$<0.001) presented reduced but still significant predictive power to overall ADHD symptoms. Although the predictive power of hyperactivity-impulsivity was slightly more reduced than the predictive power of inattention to overall symptoms in the simultaneous model, we could not argue about any differences in the impact of inattention or hyperactivity-impulsivity on general ADHD symptoms. Actually, the effect of hyperactivity-impulsivity in overall ADHD symptoms trough inattention was exactly the same effect of the opposite pattern ($z$=7.18, p<0.001). Therefore, a possible predictive direction of inattention and hyperactivity-impulsivity within children remained undetermined in our sample. Thus, at this point we could not suppose whether maternal hyperactivity-impulsivity influence children inattention or children hyperactivity-impulsivity

differently. Children inattention and hyperactivity-impulsivity shared great part of their variance ($R^2$=0.31, $F$(1, 115)=51.60, $p$ <0.001). Then, it is possible that maternal hyperactive-impulsive symptoms influence essentially the strong common portion of children ADHD dimensions.

The relationship between maternal and children hyperactive-impulsive symptoms was completely attenuated ($B$=0.23, $p$=0.02 *vs*. $B$=0.14, $p$=0.09) when children inattention was taken into account. This simple mediation model with maternal hyperactive-impulsive symptoms as predictor and children inattention and hyperactivity-impulsivity respectively as mediator and outcome variables was significant (z=2.96, $p$=0.009). In turn, the direct influence of maternal hyperactivity-impulsivity on children's inattentive symptoms was also reduced when children hyperactive-impulsive symptoms were taken as a mediator of this relationship ($B$=0.26, $p$=0.003 *vs*. $B$=0.14, $p$=0.09). This model had a z effect of 2.37 ($p$=0.02). Thereon, maternal hyperactive-impulsive symptoms seemed to mainly influence the shared variance between children ADHD symptoms dimensions. However, the simple mediation model testing children inattention as mediator provided a stronger effect. That is, specific factors related to children inattention and not only to the shared factors between children ADHD dimensions might explain the maternal symptoms influence on children hyperactive-impulsive symptoms. Figure I presents a hypothetical serial multiple mediator model of maternal ADHD symptoms influence on children ADHD symptoms that integrate our results.

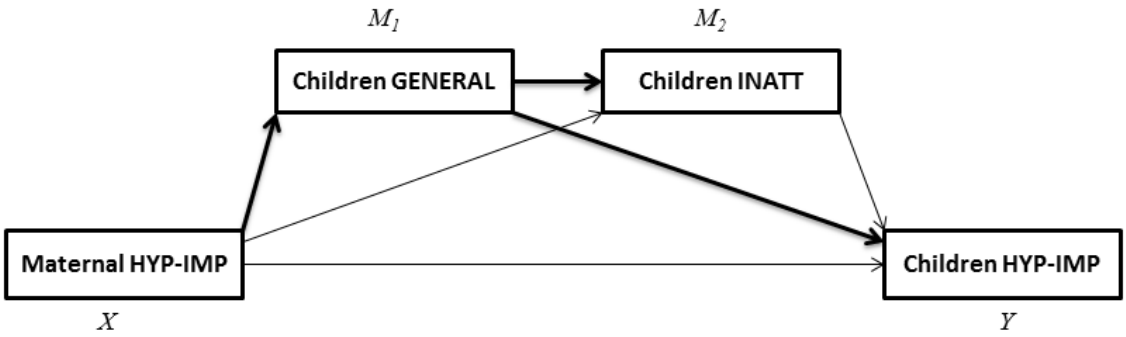


**FIGURE 3.1. Hypothetical serial multiple mediator model of maternal ADHD symptoms influence on children ADHD symptoms**

X= Predictor; Y= Outcome; $M_1$=Mediator 1; $M_2$=Mediator 2. The influence of maternal symptoms on children's symptoms was mainly exerted by the hyperactivity-impulsivity dimension. That influence is primary accounted for by shared variance within children ADHD inattention and hyperactivity-impulsivity ("general factor"). Additionally, specific children inattentive variance account for by some of the influence of maternal hyperactivity-impulsivity on their offspring hyperactive-impulsive symptoms.

We investigated whether children age and gender, and family socioeconomic status were significant intervenient factors of the mother-children symptoms association. When the mediation

model was separately conducted across age groups with a 5000 bootstrapped method, we observed an increase of the mediation effect with age (6-7 years: z=0.88, *p*=0.39; 8-10 years: z=1.09, p=0.28; 11-16 years: z=2.37, *p*=0.02). The mediation model was moderately stronger for female gender (z=1.94, *p*=0.05) than for male gender (z=1.35, *p*=0.18), and higher in low SES context (z=2.18, *p*=0.03) than in high SES context (z=0.64, *p*=0.52). The same happened for maternal education level: the group with the lower maternal education level presented the higher effect on mediation model (7-11 education years: z=2.18, *p*=0.03; 11-16 education years: z=1.11, *p*=0.27; 16-16 education years: z=0.21, *p*=0.83). Thus, it is reasonable to infer that children age and gender, and family socioeconomic status were important factors of maternal hyperactive-impulsive symptoms influence on children hyperactivity-impulsivity through children inattention (and shared variance).

**3.4 DISCUSSION**

The goal of the current study was to investigate how parental ADHD-related symptoms influence the same symptoms on their offspring, supposing a primarily parent influence on children hyperactivity-impulsivity through children inattention. This was done exploring the relationship between inattentive and hyperactive-impulsive domains by mediational analysis using maternal self-reported ADHD-related symptoms and data on offspring ADHD-related symptoms from a school-based sample.

In this sample, about a quarter of the variance in offspring ADHD symptoms were explained by maternal behavior. However, only maternal hyperactive-impulsive scores significantly predicted scores on both offspring ADHD-related domains. Even for children's inattentive symptoms maternal inattention seemed to had only an indirect effect that was accounted for by maternal hyperactivity-impulsivity. Because ADHD has a strong genetic connection, it was expected that maternal behavior would be a robust predictor of children behavior (Gillis, Gilger, Pennington, & DeFries, 1992; Larsson et al. 2006; Larsson et al.2013; Levy, Hay, McStephen, Wood, & Waldman, 1997; Morrison, & Stewart, 1971; Sherman, Iacono, & McGue, 1997; Schultz et al. 2006; Sherman et al., 1997; Stawicki, Nigg, & von Eye, 2006). The more interesting, however, was to find maternal hyperactive-impulsive dimension as a major source of maternal influence on children overall ADHD symptoms. This probably reflects additive genetic influences on ADHD that increase parent-child similarities and are more related to hyperactive-impulsive symptoms than to inattentive symptoms (Ilott, Saudino, Asherson, 2010; Larsson et al., 2013; Nikollas, & Burt, 2010; Sherman, McGue, Iacono, 1997). Shared environmental influences also generally result in similarities

between relatives and may moderately contribute to several developmental disorders, but ADHD exceptionally almost not suffer shared environmental influences (Burt, 2009; Burt, 2010; Burt, Larsson, Lichtenstein, & Klump, 2012). On the other hand, more etiological heterogeneity of inattention symptoms might act to decrease genetic covariation between parents and their children. This has relevant implications. Due to differences between inattentive and hyperactive-impulsive dimensions, particularly in cognitive and functional domains (Eiraldi, Power, & Nezu, 1997; Fischer, Barkley, Edelbrock, & Smallish, 1990; Gaub & Carlson, 1997; Maedgen & Carlson, 2000; Schmitz et al., 2002) it was expected that research with parent-child designs (e.g., to study endophenotypes) would be more assistant for that characteristics closely related to hyperactivity-impulsivity (e.g., Nikollas, & Burt, 2010). On the other hand, despite its small effect, maternal hyperactive-impulsive symptoms were more associated to children inattention than to children hyperactivity-impulsivity. It is worth mentioning that when we are working with ADHD symptoms as two specific dimensions namely inattention and hyperactivity-impulsivity we must consider that a great amount of these domains is shared between each other (Willcutt et al, 2012). Thus, it is difficult to look at an effect that is exclusively accounted for by one ADHD dimension. In fact, we are probably looking into shared underlying mechanisms in addition to specific underlying mechanisms (Stawicki, Nigg, & von Eye, 2006; Toplak et al., 2012). However, it is reasonable to think about parent hyperactivity-impulsivity as a major source of influence on overall ADHD symptoms.

We hypothesized that children's inattentive symptoms could be more related to the overall ADHD symptoms and so account for the influence of parent ADHD symptoms on children hyperactivity-impulsivity because 1) heritability of hyperactivity-impulsivity increases as a linear function of the number of inattentive symptoms, and 2) general mechanisms associated to hyperactivity-impulsivity are closer related to inattention. However, the single contribution to overall symptoms were just a little higher for inattention than for hyperactivity-impulsivity ($\beta$ difference=0.04). When both dimensions interacted to predict overall ADHD symptoms, we observed almost equivalent reduction of their associations (a reduction of $\beta$ =0.29 to inattention, and of $\beta$ =0.34 to hyperactivity-impulsivity). These results indicate that some variance from inattentive symptoms accounts for by hyperactive-impulsive symptoms predictive power for overall symptoms and vice-versa which nearly correspond to the shared variance between children ADHD dimensions (31%) and is the why we observed both predictive powers reducing. Developmentally ADHD symptoms are caused by several factors operating in a highly complex manner which result in vast heterogeneous phenotype and to

understand how inattentive and hyperactive-impulsive symptoms interact is of utmost importance (Archer, Oscar-Berman, & Blum, 2011). But investigations may be misleading without consideration about shared variance. What has been seeing is that a hierarchical model with one general factor and two additional specific factors better represent covariance between ADHD symptoms with higher correlations between these specific factors with the general factor than one each other (Dumenci, McConaghy, & Achenbach, 2004; Martel, Von Eye, & Nigg, 2010; Normand, Flora, Toplak, & Tannock, 2012; Toplak et al., 2009; Toplak et al., 2012). Thus, to find specific contributions of both ADHD behavioral dimensions would be more useful to isolate these dimensions from their general factor (which was not possible in that study due to lack of statistical power).

The influence of maternal hyperactive-impulsive symptoms on children ADHD symptoms was strongly accounted for by the shared variance between both children ADHD symptom domains. Therefore, it is likely that maternal symptoms influence on children ADHD symptomatology primarily occurs through shared paths between inattentive and hyperactive-impulsive symptoms. However, even considered the large shared variance observed within children ADHD symptom domains, children inattentive symptoms seemed to provide additional and specific pathway to maternal influence on children hyperactive-impulsive symptoms. The mediation model with children's inattentive symptoms as a mediator showed higher effect than the model with children hyperactive-impulsive symptoms as a mediator (moderate additional effect: $z=0.59$). That is, inattention might be a primarily source of influence for maternal predictive power of children ADHD behavior. Based on these results we are proposing a hypothetical serial multiple mediator model suggesting two mediators for maternal influence. The first and much stronger mediator was the shared variance between children ADHD symptom dimensions (that we clustered as "general factor") and the second and weaker was specific children inattentive dimension. A serial multiple mediator model at behavioral level is consistent with the usual ADHD sample heterogeneity that arises from etiological and phenotypic complexity (Bearden, Reus, & Freimer, 2004; Tsuang, & Faraone, 2000). Cognitive endophenotypes are more likely to reflect the activity of underlying ADHD causal pathways nearly to behavioral level (Doyle et al., 2005; Goos, Crosbie, Payne, & Schachar, 2009; Kebir, & Joober, 2011). Cognitive models stressing the possibility of multiple etiological pathways to ADHD have shown that cognitive ADHD underpinnings may be separable (Nigg, & Casey, 2005; Sergeant, 2000; Sonuga-Barke, 2002, 2003, 2005; Sonuga-Barke, Bitsakou, & Thompson, 2010). Also, different neurobiological pathways associated with different cognitive deficits may independently lead to ADHD symptoms (de Zeeuw,

Weusten, van Dijk, van Belle, Durston, 2012). ADHD involves deficits in both “cool” and “hot” executive functions which are mediated by several neural networks (mainly fronto-striatal and fronto-cortical neural networks) (e.g., Cubillo, Halari, Smith, Taylor, & Rubia, 2012). However, inhibitory control ability likely presents a particularly interesting index of shared genetic risk in ADHD (de Zeeuw, Weusten, van Dijk, van Belle, Durston, 2012; Goos, Crosbie, Payne, & Schachar, 2009; Sonuga-Barke, Bitsakou, & Thompson, 2010). Future studies should investigate how cognitive underpinnings of ADHD may explain parent influence on ADHD symptomatology through shared and specific pathways.

Our data suggested that parent-child similarities on ADHD may be stronger for older children (closely to early adolescence and beyond) and for female children. Genetic influences (the main source of parent-child similarities in ADHD symptomatology) are typically smaller in childhood and increase over time changing heritability estimates for many phenotypes (Bergen, Gardner, & Kendler, 2007; Lyons et al., 1995; McGue et al., 1993). Toplak et al. (2012) suggested that developmental changes in both ADHD dimensions (i.e., decreasing rates of hyperactivity-impulsivity and more stable rates of inattentive symptoms) might account for different genetic effects observed across ages. Also, ADHD symptoms in female gender could be more homogeneous in origin with higher genetic effects accounting for their etiology (Goos et al., 2007; Hawi et al., 2005; Rhee et al., 1999). On the other hand, why socioeconomic status is a risk factor for ADHD remains more controversial. Some studies have suggested that genetic influences may be smaller in high-risk or disadvantaged environments (Burt, McGue, Demarte, Krueger, & Iacono, 2006; Plomin & Daniels, 2011; Turkheimer, Haley, Waldron, D’Onofrio, & Gottesman, 2003; Tuvblad, Grann, & Lichtenstein, 2006). As well, it is still hard to recognize whether socioeconomic status is only a secondary source of influence on ADHD given parental symptomatology associations with SES (i.e., SES as an outcome and not a primary source of influence) (Biederman et al., 2002; Dohrenwend et al. 1992; Faraone et al. 1999). However, Lasky-Su et al. (2007) experimentally observed that relationship between low SES and ADHD could be explained by genetic factors with SES modifying the effect of specific genes to increase or decrease the likelihood of ADHD. Additional useful characteristics applied on our study that may increase power to find parent-child similarities is to work with continuous measures of ADHD normally distributed in a *continuum* of severity since nonshared environmental influences may be more etiologically salient for those with more disturbed functioning and so provide increase of heterogeneity and complexity (Burt, 2009; Neale, Eaves, & Kendler, 1994).

*3.4.1 Limitations*

This study has several limitations. First, we relied on a single type of informant (i.e., parent-reports) to assess ADHD-related symptoms and additional sources of information are needed to control for shared variance. Maternal reports of children behavior usually lead to high genetic influences and in our sample only 11% of children questionnaires were reported by fathers and not by mothers. Paternal reports usually increase probability of shared environmental influences, but ADHD exceptionally almost not suffer shared environmental influences which may decrease biases from parent report (Burt, 2009; Burt, Larsson, Lichtenstein, & Klump, 2012; Burt, McGue, Krueger, & Iacono, 2005). Child self-reports would be an additional tool despite controversies about validity of this way to measure ADHD symptoms (Barkley, 2006; Burt, Larsson, Lichtenstein, & Klump, 2012; Hart et al. 1994; Jensen et al. 1999). Maternal self-report measure also could be a problem since usually adults underreport the severity of their ADHD symptoms, decreasing estimates of genetic influences and so similarities with their offspring (Larsson et al., 2013; Saviouk et al. 2011).

In addition, we did not carry out structured psychiatric interviews with parents and children to evaluate prevalent ADHD cases in this population. We took a dimensional approach to evaluate ADHD-related symptoms and included a non-clinical population of parents and children from only one elementary school. Also, our sample ranged in age from 6- to 16-years old. So future studies should seek to extend these results to diagnostic data and different age ranges to clarify how these results may generalize to more deviant populations. Another important limitation of our study was the small sample size a common issue in epidemiologic and clinical research. Interactive models increase (especially due to multiple comparisons in our study) necessity for large sample size since as sample size becomes smaller statistical tests becomes less conservative (Preacher, & Hayes, 2004; Vittinghoff, Sen, & McCulloch, 2009). That said, the serial multiple mediator model of maternal ADHD symptoms influence on children's ADHD symptoms presented here had to be carefully interpreted as a more theoretical model.

*3.4.2 Conclusion*

In conclusion, our findings suggest that the influence of maternal symptoms on children's symptoms was mainly exerted by the hyperactivity-impulsivity dimension. That influence was primary accounted for by shared variance within children ADHD inattention and hyperactivity-impulsivity

(“general factor”). Additionally, children inattentive variance account for by some of the influence of maternal hyperactivity-impulsivity on their offspring hyperactive-impulsive symptoms. Such results encourage research to elucidate the bases of common and specific variances of ADHD dimensions. Further studies are needed to confirm these results and ensure that our findings can be extended for other populations.

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**4 - ADHD Inattentive Symptoms Mediate the Relationship between Intelligence and Academic Performance in Children Aged 6–14**

*ADHD, Intelligence, and Academic performance*

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***Abstract***

**Objective:** Since the etiology of academic problems in ADHD is still unclear, this study aimed to investigate whether ADHD symptoms mediate the influence of general intelligence on spelling and arithmetic performance. **Methods:** Sixty-two children with ADHD and 33 age-matched typically developing students were evaluated with the Raven's Colored Progressive Matrices and a Brazilian School Achievement Test. Dimensional ADHD symptomatology was reported by the children's parents. **Results:** Statistical mediation analyses showed that the influence of general intelligence on spelling and arithmetic performance occurred through behavioral inattention. **Conclusion**: Our results suggest that general cognitive abilities have an important role on ADHD academic performance. Therefore, early identification of general intelligence and inattentive scores is a major concern to prevent impaired academic performance and future difficulties in functioning.

***Keywords***

*Academic performance, Attention-deficit/hyperactivity disorder, Inattention, Intelligence, Mediation*

**4.1 INTRODUCTION**

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder of childhood identified by cognitive-behavioral deficits.[1] Studies which adopted factor analysis of the core symptoms have shown that ADHD is characterized at the behavioral level by hierarchically inter-related domains: a general ADHD dimension and distinct traits of inattention and hyperactivity-impulsivity.[2,3] Impairments in several specific cognitive domains are related to ADHD, including response inhibition, working memory, short-term memory, processing speed, vigilance, and response variability.[4] Impaired global intellectual functioning is also observed in ADHD.[5] The ADHD mild intellectual inefficiency may reflect their multiple specific cognitive deficits as long as intelligence describes the strong common core shared between cognitive domains.[6-10] Both cognitive and behavioral deficits in ADHD have an important impact on patient's functionality and knowledge of how general intelligence and ADHD symptoms are related to ADHD outcomes is of extreme relevance.[6,11]

Poor academic performance is a common feature of children with ADHD, particularly in written language and mathematics.[12-14] Although hyperactive–impulsive symptoms are associated with academic failure, behavioral inattentive symptoms are probably the core source of poor academic performance as an associated characteristic of ADHD.[4] Reading and math abilities show stronger phenotypic and genetic associations with the inattentive dimension than to the hyperactivity–impulsivity dimension.[15] Additionally, this genetic association between hyperactivity–impulsivity and academic performance might be more related to the shared genetic influences between ADHD behavioral traits.[15] Moreover, the common inversely correlation between neuropsychological domains and hyperactivity-impulsivity do not remains significant when inattention is controlled.[4] Regardless inconsistencies about the nature of the relationship between cognitive and behavioral ADHD aspects are reported,[16] the cognitive characteristics themselves are strongly related to academic success.[17] Intelligence level is also one of the most predictive factors of school performance.[9] Since cognitive endophenotypes are likely to reflect the activity of underlying ADHD causal pathways nearly to the behavioral level [19, 20] it is possible that the inattentive dimension accounts for by ADHD influence on the educational level. However, few studies addressed how cognitive aspects and behavioral dimensions of ADHD impact the academic performance.

ADHD, general cognitive ability, literacy, and mathematics disabilities are heritable, and their association may primarily be explained by shared genetic influences.[15, 20] Nevertheless, why this association occurs remain controversial. At the genetic level, moderate to high heritability *have been*

*found* for all cognitive and behavioral traits, but many genes with small effects are involved and it is feasible that the same genes affect more than one trait (pleiotropy).[20] Therefore, the same genetic influences not necessarily result in related cognitive and behavioral traits.

Previous studies have found no impact of intelligence level in ADHD symptoms influence on school achievement as there were no significant changes in academic performance after including IQ as a covariate in the predictive models.[21,22] On the other hand, cognitive impairment may lead to more severe ADHD symptoms, suggesting a bidirectional relationship between these domains in ADHD. [23,24] Still, these results are not necessarily opposites. When strongly associated variables are taken together and simultaneously in predictive models (e.g., regression models) some predictors could appear not exert a significant influence on outcomes. However, when the same excluded variable is analysed as a unique predictor it may show a strong predictive power. Then, it suggests that its effect on the outcome is indirect by another predictor (i.e., a mechanism).[25] This indicates that the effect of cognitive variables as intelligence on school performance in ADHD may be mediated by their behavioral symptoms. However, to the best of our knowledge, there is no study so far that directly examined this mediation model at the phenotypic level.

Therefore, we aim to test whether there is a mediational relationship between intelligence referred to as *g* and ADHD symptoms influence on written language and mathematic performance. Since intelligence and ADHD symptoms might have a bidirectional influence, we will test two models changing the predictive and mediation positions of these variables. The present study also addresses if the influence of behavioral inattention and hyperactivity-impulsivity on academic performance are specific and direct for both dimensions or indirect through one of this dimensions. These mediation models have potential to better explain how general intelligence and ADHD symptoms predict school performance. ADHD is thought to affect approximately 5% of the population and have a profound effect on educational outcomes.[1] However, the relationship between ADHD symptoms and school performance is further evident when regarded as continuous traits in population samples.[26] That said, our investigation comprises both ADHD and typically developing children. Considering that the magnitude of ADHD symptoms is different between genders and social class[27,28] we also investigated to which extent our models were dependent of these variables in this study.

## 4.2 METHODS

### *4.2.1 Participants*

Sixty-two children with ADHD (age range: 6-to-14 years old) were recruited from an ongoing study conducted at Clinic Hospital - Federal University of Minas Gerais, Belo Horizonte, Brazil. This study was approved by the local Ethics Committee. Participants of the clinical group underwent a semi-structured psychiatric diagnostic interview with the Brazilian version of the K-SADS-PL[29] and the diagnosis of ADHD was done following the DSM-IV criteria (4th ed. DSM-IV).[30] The group subtypes consisted of 19 children with Inattentive Subtype (ADHD-I), 3 with Hyperactive Subtype (ADHD-H), and 40 with Combined Subtype (ADHD-C). A total of 33 ADHD participants (53%) met criteria for comorbid psychiatric conditions including Oppositional Defiant Disorder (n=27), and Mood or Anxiety Disorder (n =12). Six from those 33 comorbid patients had both ODD, and Mood or Anxiety Disorder conditions. All families of ADHD children spontaneously searched the Clinic Hospital because of problems with externalizing and inattentive behaviors and no child was under any pharmacological treatment at the time of assessment.

Thirty-three age-matched typically developing (TD) students with no evidence of psychiatric or neurological disorders were recruited from two public elementary schools with similar socioeconomic background from ADHD patients. Subjects were excluded if they had a history or current evidence of psychosis, autism, brain disorders, and any genetic or medical disorder associated with externalizing behavior that might mimic ADHD, or general intelligence measured by Raven's Colored Progressive Matrices below the 6th percentile.

*4.2.2 Measures and Procedures*

*4.2.2.1 Socioeconomic status:* Socioeconomic status was assessed using the Brazilian Criterion of Economic Classification (CCEB) according to the Brazilian Research Enterprises Association.[31] The CCEB estimates the purchasing power of families living in urban areas, and it was answered by the parents. It includes 9 items that assess the available resources at home and 1 item that evaluate the education level of the householder, resulting in a scale ranging from 0 to 46 points. Families categorized into high class (23 to 46 points) have monthly incomes ranging from U$1300 to U$4712, and families categorized into low class (0 to 22 points) have monthly incomes ranging from U$380 to U$825. In this study, scores varied from 6 to 33 (M=20.19; SD=5.11) with 91% of families at the low class reaching a monthly income between U$504 to U$740, and 65% of families at the high class with a U$1166 average gross family income. The average number of people per household was 4.71(SD=1.94).

*4.2.2.2 ADHD symptom assessment:* parents completed the Brazilian version of the Swanson, Nolan, and Pelham – version IV (SNAP-IV)[32] for evaluation of ADHD symptoms in their children. SNAP-IV is an 18-item measure, each of which is rated from 0 to 3. The sum of the first 9 items of this scale describes the total level of inattentive behaviors and the sum of the last 9 items reflects hyperactive-impulsive behaviors.

*4.2.2.3 Intelligence assessment:* general intelligence was assessed with the Brazilian version of Raven's Colored Progressive Matrices (CPM).[33] It is an established non-verbal test of inductive reasoning that is often regarded as a good marker of general intelligence.[9]

*4.2.2.4 Academic assessment:* to assess academic performance we carried out two subtests of the Brazilian School Achievement Test (SAT):[34] single-word spelling, and arithmetic. The single-word reading subtest was not included in this study due to lack of appropriate normative data for the school population.[35] The SAT subtests assess academic performance according to the expected educational achievement from the 1$^{st}$ to the 6$^{th}$ grades. The spelling subtest consists of 34 single words that are read by the examiner and must be written by the children, presented in a gradual increase of difficulty. The arithmetic subtest is comprised of 38 calculations of varying degrees of complexity. Three calculations are orally presented (a simple single digit addition, a simple single digit subtraction and a comparison of two numbers), and 35 calculations must be solved and registered, including addition, subtraction, multiplication, calculation of fractions, and exponentiation. Each correct spelled word and math solved problem is scored with 1 point. Reliability coefficients (Cronbach α) of SAT subtests are 0.93 or higher.[34]

*4.2.2.5 Data Analysis*

Prior to all analyses, we calculated the z-scores for Raven's CPM, spelling, and arithmetic data, using the age-stratified population-based norms for Raven's CPM[33] and grade-stratified population-based norms for the Brazilian SAT subtests.[35] We carried out a Student t test for independent samples to assess differences in socio-demographic data and scores on the Raven's CPM, and Brazilian SAT between ADHD and TD students. Chi-square tests were used to assess differences in the frequency of dichotomous variables. We calculated effects sizes of the differences observed between groups (Cohen's *d* and *Phi* coefficient for continuous and dichotomous variables, respectively).

The mediation models were tested with all subjects together (dimensional analysis). In general, a variable *M* is considered a mediator if (1) *X* (predictor) significantly predicts *Y* (outcome), (2)

*X* significantly predicts *M*, and (3) *M* significantly predicts *Y* controlling for *X.* [25] This means that, in a simple mediation model, all variables must be related. Thus, the association of intelligence (*X*), ADHD symptomatology (inattention, and hyperactivity-impulsivity, separately) (*M*), and academic performance (*Y*) was investigated by a resampling approach of Pearson correlation (*k*=5000). Multiple regression analyses were done to evaluate the mediation effect of behavioral ADHD symptoms on the relationship between intelligence and academic performance. Spelling or arithmetic scores were the outcomes variables on these analyses. First, the direct effects of intelligence (Raven's CPM), and ADHD behavior on academic performance were individually estimated. Then intelligence and ADHD symptoms were entered simultaneously in one step, in the linear regression by the forced-enter method to test the indirect effect of ADHD symptoms (*M*) on academic performance (*Y*) controlling for intelligence (*X*). The Sobel test was performed to determine the size and significance of the indirect effect compared to the direct effect (the change was reported as a z-score effect). Since the intelligence and ADHD symptoms association might be bidirectional, we also tested the size and significance of the indirect effects with ADHD symptoms as the predictor variable (*X*), and intelligence as the mediator (*M*).

To determine whether or not the mediation effect remains constant (homogeneous) across ADHD and TD children, different genders, and SES we carried out a moderated-mediation analysis.[36] When the strength of the relationship between two variables is dependent on a third variable, moderation is said to be occurring.[36] This means that the regression weight of *Y* on *X* varies as a function of *W* (moderator). The moderated-mediation models focus on the estimation of the extent to which an indirect effect of some causal agent *X* (intelligence) on some outcome *Y* (academic performance) through a mediator *M* (ADHD symptoms) depends on a moderator *W* (group, gender, and SES in our study). The significance for conditional indirect effect was assessed by a bootstrapping strategy. Then, for hypothesis testing, the null hypothesis of no indirect effect was rejected at the$\alpha$=0.05 level of significance if 0 (zero) lies outside the Confidence Interval (CI=95%). To improve the percentile-based CIs we used a bias-correction method (because the sampling distribution of the conditional indirect effect should not be assumed normal). Simple regressions of *Y* on *X* at conditional values of *W* were performed, but only the size and significance of direct and indirect effects for each condition were reported.

Moderation analysis was also performed to test whether the influence of ADHD symptoms on academic problems was conditioned to intelligence level. We estimated an OLS regression model

predicting academic performance from intelligence, ADHD behavior, and their product. To avoid redundant results, however, only the conditional effects ("simple slopes") of intelligence on academic performance estimated using the "pick-a-point" approach with the sample mean and plus and minus one standard deviation from the mean representing "average", "high," and "low" intelligence level, respectively, were reported.

The Statistical Package for Social Sciences (SPSS) software, version 20.0, was used for statistical analysis. Moderated-mediation analyses were done using a macro (PROCESS) developed for SPSS by Hayes[36] to model mediation, moderation, and conditional processes.

## 4.3 RESULTS

### *4.3.1 Descriptive analysis*

Table 1 shows socio-demographic characteristics, the scores on Raven's CPM, and Brazilian SAT for the overall sample and according to diagnostic groups. There were no statistically significant differences on age or SES between groups. The frequency of males was significantly higher in the ADHD group. As expected, the ADHD group had higher scores on SNAP-IV inattentive and hyperactive-impulsive scores. ADHD group had worse performance on Raven's CPM, spelling, and arithmetic compared to typically developing students. As presented in table 2, general intelligence was significantly related to inattentive symptoms, spelling, and arithmetic performance, but not with hyperactivity-impulsivity. Therefore, only the inattentive dimension was tested in mediation models.

### *4.3.2 Relationship between Intelligence and ADHD dimensions on Spelling Performance*

Table 3 presents all effects on academic performance. Intelligence and inattention had significant direct effects on spelling performance. When simultaneously entered in the regression model intelligence and inattention were still significant predictors accounting for by 25% of spelling scores' variance. However, both measures were less influent when taking together with a higher decrease in intelligence predictive power. The mediation model testing the influence of intelligence on spelling performance through inattention was the only with a significant effect. The mediation analysis for the opposite model, i.e., the influence of inattention on spelling performance through intelligence was marginally significant ($p$=0.07). Therefore, the results suggest that behavioral inattention was a partial mediator of intelligence influence on spelling performance.

We tested whether the significant mediation model was conditioned to diagnostic groups (ADHD *vs* TD), gender or SES. This data is presented in table 4. A 95% bootstrap confidence interval for the conditional indirect effect was entirely above zero (significant) only for students at the low SES group. Thus, the impact of intelligence level on spelling performance through phenotypic inattention was further evident for low SES children in our sample. However, the direct effect of intelligence on spelling performance (i.e. independent of inattentive behavior) was stronger for typically developing children, and girls, besides for students at the low SES group.

**Table 1**. Participants' characteristics and group comparisons

| | **All (n=95)** | **ADHD (n=62)** | **TD (n=33)** | ***t*/$\chi^2$** | ***p*** | ***d*/φ** |
|---|---|---|---|---|---|---|
| Age (years) *M(SD)* | 9.62 (1.66) | 9.60 (1.77) | 9.67 (1.45) | 0.19 | 0.850 | -0.04 |
| Male *n*(%)** | 60 (63%) | 49 (79%) | 11 (33%) | 19.33 | 0.001 | 0.45 |
| High SES *n*(%) | 30 (32%) | 20 (32%) | 10 (30%) | 0.10 | 0.750 | 0.03 |
| **ADHD subtype** | | | | | | |
| Inattentive *n*(%) | 19 (20%) | 19 (31%) | - | - | - | - |
| Hyperactive *n*(%) | 3 (3%) | 3 (5%) | - | - | - | - |
| Combined *n*(%) | 40 (42%) | 40 (64%) | - | - | - | - |
| **Psychiatric Comorbidity** | | | | | | |
| Oppositional Defiant Disorder | 27 (28%) | 27 (44%) | 0 (0%) | - | - | - |
| Mood/Anxiety Disorder | 12 (13%) | 12 (19%) | 0 (0%) | - | - | - |
| **ADHD Behaviors** | | | | | | |
| Inattention *M(SD*** | 15.85 (7.87) | 20.53 (4.00) | 7.06 (5.43) | 11.51 | 0.001 | 3.00 |
| Hyperactivity-impulsivity *M(SD*** | 13.84 (8.12) | 18.40 (5.79) | 5.27 (3.70) | 11.80 | 0.001 | 2.57 |
| **Intelligence** $M_{z\text{-score}}$(SD)* | 0.20 (0.87) | 0.04 (0.90) | 0.50 (0.75) | 2.52 | 0.010 | -0.55 |
| **Academic Performance** | | | | | | |
| Spelling $M_{z\text{-score}}$(SD)** | 0.07 (1.10) | -0.23 (1.05) | 0.65 (0.96) | 4.02 | 0.001 | -0.87 |
| Arithmetic $M_{z\text{-score}}$(SD)** | -0.13 (1.23) | -0.43 (1.27) | 0.42 (0.96) | 3.38 | 0.001 | -0.73 |

*Note:* TD=typically developing students
*Difference was significant at p<0.01; **Difference was significant at p<0.001.

**Table 2.** Correlations between all Independent variables and the Outcome variables (Standard Errors in parentheses)

| **Measures** | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| 1. Intelligence | -0.25*(0.10) | -0.08 (0.10) | 0.37** (0.08) | 0.27* (0.10) |
| 2. Inattention | | 0.74** (0.05) | -0.45** (0.08) | -0.36** (0.08) |
| 3. Hyperactivity-impulsivity | | | -0.36** (0.09) | -0.26* (0.09) |
| 4. Spelling | | | | 0.62** (0.07) |
| 5. Arithmetic | | | | |

*Note.* 5000 bootstrap samples. *Correlation was significant at the 0.05 level (2-tailed). **Correlation was significant at the 0.001 level (2-tailed).

*4.3.3 Relationship between Intelligence and ADHD dimensions on Arithmetic Performance*

Significant direct effects on arithmetic performance were observed for intelligence and inattention, individually. In the full model, however, only behavioral inattention remained a significant predictor accounting for by 12% of variance on arithmetic performance. The difference between the direct and indirect effects was significant, suggesting that the influence of intelligence on arithmetic performance was completely mediated by inattentive symptoms. For arithmetic performance only, this mediation model (and not the model testing intelligence as mediator instead the inattentive problems) had a significant effect size.

Similar to the mediation model for spelling performance, the moderated-mediation analysis for arithmetic performance was significant only for students at the low SES group. This means that behavioral inattentive phenotype might be a mechanism of intelligence influence on arithmetic performance especially for children at the low SES in this sample. Even the direct effect of intelligence on arithmetic performance was only significant for children with low SES but seems to be homogeneous between ADHD and TD children, and also between genders.

Figure 1 presents the mediation model of intelligence influence on academic performance through behavioral inattention.

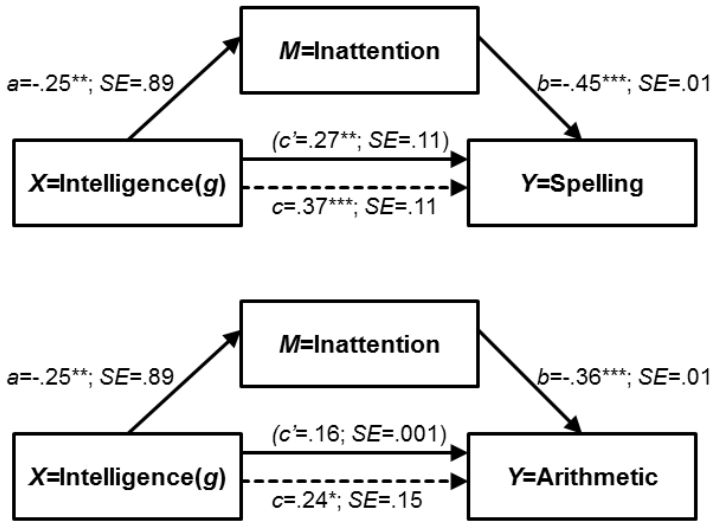


**FIGURE 4.1. Mediation model of general intelligence influence on academic performance through inattentive symptoms in ADHD dimensional behavior**

X= Predictor; Y=Outcome; M= Mediator. General intelligence (*c*) and inattentive symptoms (*b*) were strong individual predictors of spelling and arithmetic performance. However, general intelligence (*c'*) had an indirect effect on academic performance through behavioral inattention (*a*). *$p$<0.05; **$p$<0.01; ***$p$<0.001

**Table 3.** Direct and Indirect Effects of Independent variables on Outcome variables and significance of Mediation Models

| Condition | Outcome (*Y*) | Predictor(s) | *β* | *t* | $SE_{boot}$ | *p*-Value | $R^2_{adj}$ | Mediation Model | z | *p*-Value |
|---|---|---|---|---|---|---|---|---|---|---|
| Individually | Spelling | Intelligence | 0.37 | 3.78 | 0.11 | <0.001 | 0.12 | *X*=Intelligence; *M*=INATT | 2.12 | 0.03 |
| | | INATT | -0.45 | -4.87 | 0.01 | <0.001 | 0.19 | *X*=INATT; *M*=Intelligence | 1.85 | 0.07 |
| Simultaneously | Spelling | Intelligence | 0.27 | 2.91 | 0.11 | 0.005 | 0.25 | | | |
| | | INATT | -0.38 | -4.16 | 0.01 | <0.001 | | | | |
| Individually | Arithmetic | Intelligence | 0.24 | 2.41 | 0.15 | 0.02 | 0.05 | *X*=Intelligence; *M*=INATT | 1.92 | 0.05 |
| | | INATT | -0.36 | -3.69 | 0.01 | <0.001 | 0.12 | *X*=INATT; *M*=Intelligence | 1.30 | 0.19 |
| Simultaneously | Arithmetic | Intelligence | 0.16 | 1.63 | <0.001 | 0.11 | 0.12 | | | |
| | | INATT | -0.32 | -3.18 | 0.02 | 0.002 | | | | |
| Individually | Spelling | INATT | -0.45 | -4.87 | 0.01 | <0.001 | 0.19 | *X*= HYP-IMP; *M*=INATT | -2.84 | 0.005 |
| | | HYP-IMP | -0.36 | -3.70 | 0.01 | <0.001 | 0.12 | *X*=INATT; *M*= HYP-IMP; | -0.42 | 0.67 |
| Simultaneously | Spelling | INATT | -0.41 | -2.97 | 0.02 | 0.004 | 0.19 | | | |
| | | HYP-IMP | -0.06 | -0.43 | 0.02 | 0.67 | | | | |
| Individually | Arithmetic | INATT | -0.36 | -3.69 | 0.01 | <0.001 | 0.12 | *X*= HYP-IMP; *M*=INATT | -2.49 | 0.01 |
| | | HYP-IMP | -0.26 | -2.54 | 0.01 | 0.01 | 0.06 | *X*=INATT; *M*= HYP-IMP; | 0.12 | 0.90 |
| Simultaneously | Arithmetic | INATT | -0.37 | -2.57 | 0.02 | 0.01 | 0.11 | | | |
| | | HYP-IMP | 0.02 | 0.12 | 0.02 | 0.9 | | | | |

*Note.* 5000 bootstrap samples. INATT= Inattention; HYP-IMP= Hyperactivity-Impulsivity; *X*= Predictor; *M*= Mediator.

**Table 4.** Conditional Direct and Indirect Effects of Intelligence on Academic Performance at levels of Group diagnosis, Gender, Socioeconomic Status, and Hyperactivity-Impulsivity

| Academic Domain | Moderator (*W*) | Group (n) | Direct effect[a] | *p*-Value | Indirect Effect[b] | $SE_{boot}$ | CI |
|---|---|---|---|---|---|---|---|
| Spelling | Group | ADHD (n=62) | 0.25 | 0.07 | 0.002 | 0.03 | -0.06-0.07 |
| | | TD (n=33) | 0.57 | 0.01 | 0.08 | 0.07 | -0.01-0.28 |
| | Gender | Male | 0.19 | 0.23 | 0.03 | 0.05 | -0.05-0.15 |
| | | Female | 0.45 | 0.01 | 0.09 | 0.07 | -0.02-0.28 |
| | SES | Low* | 0.37 | 0.01 | 0.17 | 0.08 | 0.05-0.36 |
| | | High | -0.07 | 0.73 | 0.06 | 0.12 | -0.15-0.34 |
| | HYP-IMP Level | Low | 0.54 | 0.01 | 0.12 | 0.09 | -0.01-0.34 |
| | | Average | 0.37 | 0.002 | 0.06 | 0.05 | -0.004-0.19 |
| | | High | 0.21 | 0.21 | -0.01 | 0.04 | -0.09-0.06 |
| Arithmetic | Group | TD | 0.18 | 0.51 | 0.06 | 0.07 | -0.01-0.28 |
| | | ADHD | 0.24 | 0.15 | 0.00 | 0.03 | -0.05-0.07 |
| | Gender | Male | 0.06 | 0.75 | 0.03 | 0.05 | -0.04-0.15 |
| | | Female | 0.37 | 0.08 | 0.09 | 0.08 | -0.02-0.28 |
| | SES | Low* | 0.34 | 0.05 | 0.14 | 0.07 | 0.03-0.34 |
| | | High | -0.31 | 0.23 | 0.05 | 0.10 | -0.12-0.29 |
| | HYP-IMP Level | Low | 0.42 | 0.07 | 0.15 | 0.11 | -0.01-0.42 |
| | | Average | 0.25 | 0.08 | 0.07 | 0.06 | -0.002-0.23 |
| | | High | 0.08 | 0.67 | -0.01 | 0.05 | -0.12-0.08 |

*Note.* 5000 bootstrap samples. [a.]Magnitude of the effect of 'Intelligence' on 'Academic Performance' as a function of the moderator; [b.]Magnitude of the effect of 'Intelligence' on 'Academic Performance' through 'Behavioral Inattention' as a function of the moderator. SES= Socioeconomic Status; HYP-IMP= Hyperactivity-Impulsivity. *The Indirect effect was significant at the 0.05 level

*4.3.4 The influence of Hyperactivity-impulsivity on Academic Performance*

Regardless of moderate direct effects of hyperactivity-impulsivity on spelling and arithmetic performance, these effects were completely reduced when inattention was inserted in the simultaneous regression models. This means that the influence of hyperactivity-impulsivity on academic performance was fully accounted for by inattentive problems. The significance and size of these mediation models are presented in table 3. In addition, we tested the hyperactivity-impulsivity as a moderator of the influence of intelligence on academic performance through behavioral inattention (see table 4) to investigate whether the strength of this indirect effect changes as a function of hyperactive-impulsive level. Both for spelling and arithmetic performance we found no conditional indirect effects. However, the direct influence of intelligence on academic performance was stronger for children at the “average” and “low” hyperactive-impulsive level groups. Children with hyperactive-impulsive symptoms at the plus one standard deviation from the mean (“high”) had no significant effect.

*4.3.5 Inattentive symptoms´ influence on Academic Performance depending upon Intelligence level*

The conditional effect of inattention on academic performance at values of intelligence is presented in table 5. The impact of inattentive problems on academic performance seems to be marginally significant for children in the "low" range of intelligence level but remains largely significant for students at the "average", and "high" intelligence levels.

**Table 5.** Conditional effect of Inattention on Academic performance at levels of Intelligence

| Outcome | Intelligence level | Effect | $SE_{boot}$ | t | *p* | CI |
|---|---|---|---|---|---|---|
| Spelling | Low | -0.04 | 0.02 | -1.90 | 0.06 | -0.08/0.002 |
| | Average* | -0.05 | 0.01 | -3.85 | <0.001 | -0.08/-0.03 |
| | High* | -0.06 | 0.02 | -3.84 | <0.001 | -0.10/-0.03 |
| Arithmetic | Low | -0.04 | 0.02 | -1.76 | 0.08 | -0.09/0.006 |
| | Average* | -0.05 | 0.02 | -3.02 | 0.003 | -0.08/-0.02 |
| | High* | -0.05 | 0.02 | -2.68 | 0.009 | -0.09/-0.01 |

*Note.* 5000 bootstrap samples. *The Direct effect was significant at the 0.01 level

**4.4 - DISCUSSION**

This study investigated how cognitive (referred as general intelligence) and behavioral features (stated as inattentive and hyperactive-impulsive symptoms) associated to ADHD impact academic performance. In agreement with previous studies, we found that ADHD children had worse performance in general intelligence and academic performance compared to typically developing students. [6,11,12,14,23] Despite some studies arguing that intelligence maybe not influence the relation between ADHD and academic performance,[21,22] the mediation analyses used in this study suggest that this could be a misinterpretation of direct and indirect effects of these constructs. We begin to demonstrate that behavioral inattention might be a mediator of the influence of general intelligence on academic performance in children. Additionally, our data indicates that this cognitive to behavioral direction is more likely than the behavioral to cognitive pathway, especially for math performance. Though it is important to emphasize that behavioral inattention was a partial mediator of intelligence influence on spelling performance. Therefore, other factors besides inattentive behavior may account for by the intelligence influence on spelling performance. The shared neuropsychological deficits between ADHD and specific learning disabilities could in part reflect the differences in this mediation model for spelling and math performance. The most consistent cognitive ability shared with ADHD and literacy abilities may be processing speed.[37,38] In its turn, math performance involves additional shared cognitive domains as working memory, visual-spatial processing, cognitive attention, and inhibition. [37-

[40] These extra shared cognitive domains with math performance are impaired in ADHD with high levels of behavioral inattentive symptoms and usually are more related with general intelligence,[4,9,41] which help us to explain why the influence of general intelligence on arithmetic performance was fully accounted for by behavioral inattention. These results suggest that treatment focusing in behavioral inattention is of utmost importance to decrease academic problems in childhood. Math performance may be especially sensitive to inattentive symptoms interventions[42] since general cognitive underpinnings of math performance are likely to fully influence performance through behavioral inattention.

We also investigated whether group features as diagnostic, gender or socioeconomic status would interfere on the significant mediation model (X=intelligence → M=inattention → Y=academic performance). We found that this model was only conditioned to the SES. Individuals with low-income level could be more severally impacted on school performance by cognitive and behavioral characteristics associated to ADHD. Low SES is a risk factor for ADHD independently of gender and other risk factors, and it is difficult to explain how SES influences ADHD or vice-versa. [43] Another complex consideration is that intelligence scores *per se* are positively correlated with family level of income, education, and other SES factors.[44] These relations complicate interpreting intelligence in psychiatry context when a preexisting intelligence difference occurs in a disorder associated with lower SES as is ADHD. Usually outcomes associated to low socioeconomic status are explained by environmental conditions or peculiar features closely related to low-income individuals as the level of education, but recent work has focusing in mental processes as a complementary explanation.[45] The continuous efforts applied in the competition for survival recourses at the low end of economic distribution could be struggle enough to decrease the cognitive resources available to guide choice and action (a strong cognitive distractor). However, this causative cognitive model might be conditioned to adulthood,[45] and the age-related aspects of the impact of SES in cognitive and behavioral development should be investigated. It is necessary to note that our sample encompasses a less diverse income range, and more than 84% of individuals are representative of the Brazilian middle class. At any rate, our study suggests that behavioral inattention evaluation should be a central target for early identification of learning problems especially for children with low SES.

Still on conditioned effects, we found that intelligence may have a more direct effect on spelling performance for typically developing learners, and for girls on spelling and math performance. Since the sample under study was selected in the ADHD behavior context, it is not possible to

generalize these direct effects beyond ADHD research. Previous ADHD investigations found that the relationship between ADHD symptoms and reading is further evident when regarded as continuous traits in population samples.[26] In turn, the relationship between ADHD and math performance is less explored.[46] Our data showed no effect of group suggesting that the relationship between ADHD symptoms and arithmetic performance would be observed equally for ADHD and TD children. A higher effect of cognitive problems on ADHD outcomes for the female gender was also previously demonstrated. Despite overrepresentation of boys over girls in ADHD, its impact is not always worse for boys than for girls.[47] In fact, higher rates of speech and language disorders have been found in girls with ADHD compared with boys.[48] Maybe there are sex differences in the etiology of ADHD, but the mechanisms underlying sex differences in ADHD remains unclear. [47,48]

Our study also provides a further step toward previous literature that indicates behavioral inattention as a core source of academic problems in ADHD. There was no residual phenotypic overlap between hyperactive-impulsive symptoms and academic performance independent of behavioral inattention, which means that academic performance association to hyperactivity-impulsivity in ADHD can fully be explained by the inattentive dimension. Studies about academic functioning in ADHD usually report no distinction between Inattentive and Combined subtypes[4] and genetic investigations have shown inattentiveness as the explanatory link of impaired academic performance in ADHD.[15] However, our data suggest that hyperactive-impulsive symptoms may have a predictive role when occur in a broad range level. At levels of hyperactivity-impulsivity until1 SD above mean (“low”, and “average”, but not higher than) the impact of intelligence on academic performance seems to be stronger (see table 4). Shared environmental influences, additionally to genetic overlapping, might be responsible for associations between hyperactivity-impulsivity and academic performance.[15] Future investigation of ADHD environmental influences perhaps brings some light to how hyperactivity-impulsivity impact academic outcomes when regarded as continuous traits in population samples.

Another weighty issue addressed here was whether the influence of inattentive symptoms on academic performance was homogeneous across intelligence level. Our study included no children with formal intellectual disabilities, but the influence of behavioral inattention on academic performance (both spelling and arithmetic) was only marginally significant for individuals at the “low” intelligence level whereas significant for “average” and “high” intelligence groups. Notwithstanding, our results do not indispensably mean that inattentive problems have no influence on academic problems

to “low” intellectual performers. Instead, it would imply that the general cognitive deficit might be strong enough to show a direct effect on academic performance independent of the inattentive level. The nature of inattentive problems at the low end of the typical intelligence distribution is even further controversial and unclear in the literature.[49] DSM-IV diagnostic criteria for ADHD have supported a Developmental Model by which the intensity of inattentive problems in Intellectual Disability (ID) has to be weighted by mental and not chronological age because inattentive phenotype is extremely frequent in ID.[30] However, this comorbidity profile might have few treatment implications. The combined treatment of stimulant medication, in addition to behavioral intervention, has been effective on ID and ADHD children. [49] Although methods of applied behavior analysis might be even more useful for comorbid cases compared to pure ADHD children.[49]

Ultimately, the most important methodological issue from this work is that it may be difficult to control for intelligence in ADHD school achievement research since intelligence effect on performance will be exerted at least in part through the ADHD inattentive dimension. Only consider intelligence scores as covariate in predictive models might be quite inaccurate.[50] Since systematic negative relationship between ADHD symptoms and intelligence exists, then controlling for differences in intelligence may remove variance that is due to ADHD in the measures under investigation.[5] Even recommend a significant discrepancy between intelligence and specific measures of academic performance in ADHD as a diagnosis criterion for comorbid learning disabilities may be problematic since 1) at least in some contexts general cognitive abilities might be etiologically associated to academic performance, and 2) specific cognitive functions intrinsically related to ADHD and school success are also powerful predictors of performance in general intelligence formal tests.[17]

*4.4.1 Limitations*

This study has limitations which should be addressed. First, we relied on a single type of informant (i.e., parent-reports) to assess ADHD-related symptoms. Other important limitation was that we used only one measure of intelligence. The Raven’s CPM involves only general aspects of reasoning, such as mental arithmetic and non-verbal reasoning. However, since other measures as the widely used Wechsler IQ tests may require knowledge of vocabulary, numbers, and arithmetic, i.e., abilities frequently impaired as outcomes in ADHD context, tests requiring only spatial and reasoning skills might be a methodological strength.[51] Further studies applying more sources of behavior

information (e.g., teacher ratings) and different measures of intelligence are needed to expand our results.

The absence of control for comorbid disorders was another weakness of our work. Psychiatry comorbid disorders are a potential factor of impact on general cognitive abilities in ADHD since comorbid groups may have lower IQ scores than pure ADHD groups.[52] We also do not exhaust possible relationship explanations. At least for language abilities, the literacy problems themselves may play a causative role on inattentive behavior, notably for children at the beginning of formal education.[53] On the other hand, our sample includes typically developing learners, and children identified as ADHD were not under any pharmacological treatment, which are major strengths of the present study.

It is well known that children with normal or even superior intellectual abilities can fail in specific academic domains,[51] but it does not exclude the fact that intelligence still one of the main predictors of school performance. We tested a "domain-general" cognitive capacity as an important source of influence on ADHD domains and academic performance. Future studies can address indirect effects of specific ADHD cognitive endophenotypes on academic performance. Processing speed, working memory, cognitive flexibility, and inhibition are preferential candidates to test the mediation model presented in this study since they are more related to general cognitive performance.[6-10,37-40] However, it is of extreme relevance also focusing in "core cognitive" domains to the best understanding of academic problems in ADHD, even though distinct etiological mechanisms may be involved.[54] For instance, independent of co-occurring dyscalculia, ADHD children show decreased numerosity processing compared to typically developing learners, but why, or when this might occur still far unclear.[55] It is worth noting that poorer cognitive performance at high levels of inattention may increase the need for special education.[56]

In conclusion, this study showed how general cognitive ability and behavioral ADHD symptoms might be related to predict academic performance. Given the importance of academic development in the future outcomes[51] their underlying mechanisms should be acknowledged.

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## 5 - CONCLUSÕES E RECOMENDAÇÕES

Na presente dissertação, apresentamos resultados de duas investigações específicas. Primeiro buscamos estudar como os sintomas maternos influenciam as dimensões comportamentais do TDAH, em seus filhos. Os resultados desse estudo sugeriram que, numa população de escolares, os sintomas de TDAH maternos respondem por cerca de ¼ da variância dos sintomas de TDAH nos estudantes. Esta forte influência se dá de modo predominante pela dimensão hiperativo-impulsiva materna que parece ser responsável essencialmente pelos fatores fenotípicos compartilhados entre as dimensões desatenta e hiperativo-impulsiva dos estudantes. Adicionalmente, foi observado que a influência dos sintomas maternos sobre os sintomas de hiperatividade-impulsividade pode ser em alguma medida indireta, sendo primariamente exercida sobre os sintomas de desatenção e secundariamente sobre os de hiperatividade-impulsividade.

O segundo objetivo geral deste trabalho foi estudar como as dimensões comportamentais do TDAH se relacionam com prejuízos no nível cognitivo trazendo impacto ao desempenho escolar. Mais uma vez, os sintomas de desatenção apresentaram um papel central: maiores prejuízos cognitivos globais poderiam levar a um nível maior de desatenção o que, por sua vez, estaria associado a um pior desempenho acadêmico. Embora os sintomas de hiperatividade-impulsividade não tenham apresentado associação significativa com o nível de funcionamento cognitivo global, quando presentes podem tornar ainda mais intensa a relação entre os sintomas de desatenção com o desempenho escolar. Os sintomas de hiperatividade-impulsividade estão usualmente mais relacionados a aspectos cognitivos afetivos como a capacidade de tomada de decisão que podem ser dissociadas de medidas de inteligência geral.[3,27] No entanto, esses aspectos cognitivos afetivos são extremamente importantes para o desempenho escolar, visto que a motivação para o estudo é um dos aspectos chave da aprendizagem.[28] Contudo, ainda não foi investigado como os aspectos relacionados à autorregulação, a tomada da de decisão e outros aspectos cognitivos afetivos relacionados à hiperatividade-impulsividade no TDAH afetam o desempenho escolar. Mesmo que neste ponto não esteja clara a origem dos problemas acadêmicos no TDAH, esses resultados apontam para o fato de que as habilidades acadêmicas devem ser avaliadas para estudantes com o transtorno tanto como parte de rotinas de triagem como integrando avaliações multidimensionais diagnósticas ou de monitoramento do tratamento. Os programas de intervenção geralmente focam apenas em uma das dimensões prejudicadas (desatenção ou desempenho escolar), no entanto,

entender os mecanismos pelos quais problemas relacionados ao TDAH e problemas de aprendizagem se relacionam é fundamental para uma intervenção empiricamente fundamentada. [14]

É bem conhecido que as diferenças peculiares às dimensões comportamentais do TDAH (desatenção e hiperatividade-impulsividade) estão entre as principais causas da heterogeneidade do transtorno o que leva a inconsistências nos achados relativos à sua etiologia, tornando extremamente difícil a previsão e atuação sobre grupos fenotipicamente mais homogêneos. Soma a essa complexidade o fato de que cada fator etiológico pode ter um desfecho distinto dependendo de fatores contextuais como idade, sexo, núcleo familiar ou social.[29] Para os dois estudos deste trabalho, características sociodemográficas se mostraram relevantes no estudo dos sintomas de TDAH numa perspectiva dimensional. No primeiro estudo, observamos que o poder da hiperatividade-impulsividade materna para prever a sintomatologia dos filhos aumenta com a idade do estudante. Esse resultado sugere que quanto mais nova a criança, menor a força de determinantes responsáveis pela semelhança mãe-criança, apontando para períodos mais promissores de modificação de sintomatologia. Embora o estudo das dimensões comportamentais do TDAH ainda se concentre em meninos, numa perspectiva dimensional fica ainda mais evidente que os sintomas de TDAH podem ser particularmente impactantes para as meninas. Outro grupo especialmente vulnerável é o de menor nível socioeconômico, sendo os anos de escolaridade das mães um bom identificador do contexto social e econômico dos estudantes.

Tem sido proposto que o uso de fenótipos mais simples como os endofenótipos podem aumentar a identificação dos mecanismos envolvidos nos transtornos psiquiátricos, portanto, a identificação de grupos fenotípicos mais homogêneos.[30] Estudos futuros devem investigar a utilidade e validade dos modelos aqui propostos empregando endofenótipos do TDAH. O delineamento usado no estudo dos endofenótipos é particularmente útil por incluir amostras não clínicas. Os transtornos do desenvolvimento podem ser melhor entendidos como extremos de características ou traços normalmente observados na população em um *continuum* de frequência e intensidade.[31-33] O estudo de características comportamentais dimensionais (fenótipo) em indivíduos com desenvolvimento típico é de extrema relevância para o entendimento desses transtornos.[34] A fidedignidade, validade e utilidade clínica da classificação categórica do TDAH está bem estabelecida,[35,36] mas existem fortes evidências mostrando também a validade preditiva do TDAH definido em termos de suas dimensões comportamentais num contínuo de gravidade dos sintomas.[37,38] Cabe destacar, contudo, que mesmo

ocorrendo fenotipicamente de forma dimensional, isso não significa necessariamente que os mesmos mecanismos influenciariam igualmente um transtorno por todo o *continuum* de gravidade.[39] Estudos que incluam populações clínicas (com o diagnóstico categórico), mas também incluam medidas quantitativas dos sintomas do TDAH (como no delineamento do estudo 2 desta dissertação) poderiam facilitar a comparação com estudos epidemiológicos.

Entre as limitações deste trabalho citamos a ausência de medidas respondidas por mais de um observador. Contudo, cabe ressaltar que no estudo de características intermediárias subjacentes ao transtorno e, principalmente, na identificação da etiologia do TDAH, a modesta correlação geralmente encontrada entre observadores pode ser, na verdade, fonte de inconsistência nos resultados.[39] De todo modo, concentrar as investigações sob a percepção de apenas um observador poderia trazer problemas em relação à fidedignidade dos resultados devido a uma série de fatores (erro de medida, inconsistência no relato dependendo de instrumento, etc.),[40] sendo necessário que novos estudos repliquem os estudos aqui propostos empregando múltiplos observadores (professores, por exemplo). O esclarecimento de diferenças fenotípicas dependentes do tipo de observador tem potencial para diminuir as inconsistências dos achados em nível molecular, visto que a discrepância observada na descrição dos sintomas de TDAH entre os observadores poderiam também indicar diferenças etiológicas.[40-42] Por exemplo, o relato de sintomas por mães usualmente oferece os maiores índices de herdabilidade no TDAH (60-91%), enquanto que o relato de professores pode gerar índices de herdabilidade apenas moderados (16-20%) se considerado dimensionalmente.[36,43,44] Outra limitação importante e que deve ser somada para a validação dos modelos aqui propostos diz sobre o delineamento. A continuidade ao longo do tempo dos sintomas de TDAH se dá principalmente por fatores genéticos que podem não ser os mesmos ao longo do desenvolvimento[45-48] o que aponta especialmente pra necessidade de estudos longitudinais para a identificação e confirmação de padrões de influência no nível fenotípico.

Nesta dissertação, foram apresentados modelos que se propõem a explicar como as dimensões comportamentais do TDAH se relacionam num nível fenotípico complexo. Esses modelos podem nos ajudar futuramente a entender como os endofenótipos do TDAH podem alterar a expressão dos diversos sintomas que caracterizariam o TDAH. Esse entendimento não apenas permite conclusões mais precisas em relação à variabilidade fenotípica desse transtorno como também poderá acrescentar informações que pautem iniciativas públicas futuras relacionadas a

procedimentos de diagnóstico, tratamento e intervenção em *clusters* fenotípicos mais específicos e de maior vulnerabilidade aos sintomas do TDAH.

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