UNIVERSIDADE FEDERAL DE MINAS GERAIS
INSTITUTO DE CIÊNCIAS BIOLÓGICAS
PROGRAMA DE PÓS-GRADUAÇÃO EM NEUROCIÊNCIAS

ANNELISE JÚLIO-COSTA

APRENDIZAGEM DA MATEMÁTICA E SUAS DIFICULDADES: MECANISMOS GENÉTICO-MOLECULARES E COGNITIVOS SUBJACENTES

BELO HORIZONTE - MG
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Dissertação apresentada ao Programa de Pós-Graduação em Neurociências como requisito parcial à obtenção do grau de Doutor em Neurociências. Área de concentração: Neurociências molecular, sistêmica, comportamental e computacional

Orientador: Prof. Dr. Vitor Geraldi Haase

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RESUMO

Há um consenso que o transtorno de aprendizagem da matemática tem um impacto na vida do indivíduo não só academicamente, mas também em relação a aspectos emocionais e sociais. Apesar do aumento do volume de pesquisas na área, existem tópicos que carecem de melhor elucidação. Os critérios diagnósticos ainda são controversos em termos de definição. Ademais temas como as bases genéticas do transtorno são pouco explorados. Desta maneira, a presente tese investigou o papel da inteligência na discriminação de grupos de crianças com e sem dificuldades de aprendizagem da matemática. Além disso, objetivou-se também pesquisar a associação entre aspectos genético-moleculares das vias dopaminérgicas (genes da COMT e DAT1) e mecanismos cognitivos (memória operacional e ansiedade matemática) subjacentes a aprendizagem da matemática. O trabalho é composto por três estudos. O primeiro trabalho discute acerca da validade do critério diagnóstico da discrepância em uma amostra de escolares. Tal estratégia define o que é transtorno de aprendizagem com base em uma diferença estatisticamente significativa entre testes padronizados de inteligência e desempenho escolar. Os resultados encontrados mostraram que a inteligência não é relevante para discriminar grupos de crianças com e sem dificuldades matemáticas. Ademais os níveis intelectuais impactaram apenas as medidas cognitivas globais, mas não as habilidades de cognição numérica. O estudo revela a fragilidade do critério da discrepância, embora a inteligência seja importante na caracterização dos perfis das crianças. Os dois últimos estudos apresentam evidências da relação entre aspectos genético-moleculares e mecanismos cognitivos da discalculia. Ambas as investigações foram realizadas com genes de atuação nas vias dopaminérgicas. O primeiro averiguou a associação dos genes da COMT e DAT1 com o desempenho em tarefas de memória operacional e desempenho escolar aritmético. Foram analisados modelos de dominância, co-dominância e heterose para os genes da COMT e DAT1 individualmente e também um modelo associativo. Nenhum efeito principal foi encontrado, entretanto interações entre gene, desempenho em tarefas de memória operacional e sexo foram identificadas. Em relação a COMT (rs4680), o melhor modelo para o sexo feminino considera uma dominância do alelo de valina, entanto nos meninos o modelo de codominância explica melhor as medidas cognitivas. Para o gene *DAT1*-3'-UTR VNTR um único efeito foi observado no modelo de dominância do alelo com 9 repetições. Por fim, o último estudo averiguou diferenças entre os grupos polimórficos da COMT val158met nos níveis de ansiedade matemática e desempenho aritmético em crianças de 7 a 12 anos, considerando também influências do sexo. Encontrou-se um efeito principal do sexo na direção de maiores níveis de ansiedade em meninas. Além disso, um efeito de interação

indicou que os meninos homozigotos para valina apresentaram níveis mais baixos de ansiedade matemática e as meninas do mesmo genótipo os níveis mais altos. Os resultados do segundo e terceiro estudo sugerem que diferentes variações genéticas envolvendo a biodisponibilidade da dopamina se associam a medidas que influenciam diretamente na aprendizagem da matemática e, ainda, que essa relação é dependente do sexo. A presente tese evidencia o quão complexa é a investigação sobre a aprendizagem da matemática no campo das neurociências cognitivas. O entendimento detalhado do perfil cognitivo de crianças com suspeita de discalculia é relevante para o diagnóstico e também para orientação das estratégias de intervenção. O estudo de aspectos genéticos da cognição numérica ainda se encontram em caráter exploratório, todavia há um direcionamento para futuras investigações no intuito de entender melhor a discalculia e assim intervir na promoção da aprendizagem e qualidade de vida de crianças com esse transtorno.

Palavras-chave: cognição numérica, inteligência, memória operacional, ansiedade matemática, catecol-o-metiltransferase, COMT, transportador de dopamina, DAT1, discalculia do desenvolvimento.

ABSTRACT

There is a consensus that mathematical learning disorder can impact one's life not only academically, but also emotional and social aspects. Despite the increasing research volume in the area, some topics still need better elucidation. Diagnostic criteria are still controversial and need better definition. Also, some subjects, such as the disorder's genetic bases, are little explored. In this way, the present thesis investigated the role of intelligence in the discrimination of children groups with and without difficulties on mathematics learning. Besides, the aim was to examine the association between genetic-molecular aspects of the dopaminergic pathway (COMT and DAT1 genes) and cognitive mechanisms (working memory and math anxiety) underlying mathematics learning. The thesis is composed of three studies. The first paper discusses the discrepancy criterion validity in a sample of school children. Such strategy defines learning disorder based on a statistically significant difference between standardized intelligence tests and school performance. The results showed that intelligence is not relevant to discriminate children groups with and without mathematical difficulties. Also, the intellectual levels impacted global cognitive measures only, having no influence on numerical abilities. Although intelligence is important in children's profiles characterization, the study revealed the fragility of the discrepancy criterion. The last two studies showed evidence of a relationship between genetic-molecular aspects and cognitive mechanisms involved in dyscalculia. Both investigations were performed with genes that act in the dopaminergic pathways. The first investigated the association of COMT and DAT1 genes with working memory tasks performance and arithmetic school achievement. Dominance, co-dominance, and heterosis models were analyzed for the COMT and DAT1 genes individually as well as in an associative model. No main effects were found. However, interactions between gene, working memory tasks performance, and gender were identified. Regarding COMT (rs4680), a valine dominant model was considered the best for females, while for boys, the codominance model explained the cognitive measures better. For the DAT1-3'-UTR VNTR gene, a single effect was observed in the 9 repeats allele dominant model. Finally, the latter study examined differences between COMT val158met polymorphism groups in math anxiety levels and arithmetic achievement in children aged 7 to 12 years, also considering sex influences. A major effect of sex was found towards higher levels of anxiety in girls. In addition, an interaction effect indicated that homozygous boys for valine had the lowest levels of math anxiety while girls of the same genotype had the highest levels. The results of the second and third studies suggest that different genetic variations involved in dopamine bioavailability are associated with measures that directly influence mathematics learning, and also that this

relation is sex-dependent. The present thesis shows the complexity of the mathematics learning investigation on cognitive neurosciences field. The detailed understanding of children's with dyscalculia suspicion cognitive profiles is relevant for diagnosis and also for the orientation of intervention strategies. The study of genetic aspects of numerical cognition is still exploratory. However, there is a direction for future investigations to better understand dyscalculia and thus intervene in the promotion of learning and life quality of children with this disorder.

Keywords: numerical cognition, intelligence, working memory, math anxiety, catechol-o-methyltransferase, COMT, dopamine transporter, DAT1, developmental dyscalculia

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LISTA DE ABREVIATURAS E SIGLAS

3'-UTR	3' untranslated region
ADHD	Attention Deficit Hyperactivity Disorder
ANS	Approximate Number System
ARMS-PCR	Tetra- primer amplification refractory mutation system-polymerase chain reaction
COMT	Catecol-Orto-Metiltransferase
DAT1	Dopamine transporter1
DD	Developmental Dyscalculia
Dis	Discrepant
MET	Metionina / Methionine
MDL	Mathematical Learning Difficulties
QI	Quoeficient of intelligence
KR-20	Kuder–Richardson Formula 20
PFC	Prefrontal cortex
MAQ	Math Anxiety Questionnaire
Non-Dis	Non-discrepant
SNP	Single nucleotide polymorphism
TA	Typical Achievement
TDAH	Transtorno do Déficit de Atenção e Hiperatividade
TDE	Teste de Desempenho Escolar
VAL	Valine
VNTR	Repetição em tandem de número variável
WISC	Wechsler Intelligence Scale for Children
WM	Working Memory

SUMÁRIO

1. **Introdução**

Boas habilidades matemáticas podem ser um diferencial na vida das pessoas em um mundo tão globalizado e tecnológico quanto o atual. Somos exigidos todo o tempo a lidar com números e operá-los, desde a avaliação de preços no supermercado ao entendimento de algoritmos para manipular melhor aplicativos. No Brasil a educação parece ir na contramão das demandas contemporâneas. As principais discussões na escola e sobre ela perpassam temas que deveriam ser da alçada individual e familiar enquanto as questões pedagógicas e o entendimento de como as crianças aprendem são negligenciadas. Dados governamentais (da ANA – Avaliação Nacional da Alfabetização) indicaram que no ano 2016, 55% das crianças brasileiras no 3º ano do ensino fundamental tinham conhecimentos insuficientes em matemática, podendo essas taxas chegarem a valores maiores em regiões como Norte (71%) e Nordeste (69%) (Saldaña, 2017, outubro, 25).

Para além das questões governamentais, sabe-se que a aprendizagem da matemática não é nada simples, envolvendo um ensino sistemático e também múltiplas habilidades cognitivas, tais como senso numérico, memória operacional, habilidades visuoespaciais e até regulação de respostas emocionais como, ansiedade (Haase et al., 2012; Kaufmann & Von Aster, 2012). Ademais faz-se necessário considerar que parte das crianças e adolescentes terão dificuldades persistentes na aprendizagem da matemática apresentando um quadro de Discalculia do Desenvolvimento, ou ainda, como no manual diagnóstico, Transtorno Específico de Aprendizagem com prejuízo na matemática (APA, 2013).

A discalculia do desenvolvimento é caracterizada por dificuldades persistentes na aprendizagem dos conceitos e procedimentos aritméticos, memorização de fatos, precisão e fluência de cálculos e ainda problemas no raciocínio aritmético. Tais dificuldades não podem ser explicadas por questões sociais, pedagógicas, sensoriais ou ainda déficits intelectuais globais (APA, 2013; Butterworth, Varma & Laurillard, 2015). A literatura internacional aponta que 3.6 a 8.0% das crianças em idade escolar têm discalculia (Desoete, Roeyers, & De Clercq, 2004; Shalev, Auerbach, Manor, & Gross-Tsur, 2000) e um estudo brasileiro recente indica uma taxa semelhante de 7.8% (Bastos et al., 2016). Considerando aspectos psicossociais, o diagnóstico de discalculia associa-se a desfechos econômicos desfavoráveis (Parsons & Bynner, 2005), assim como transtornos emocionais e comportamentais (Auerbach, Gross-Tsur, Manor & Shalev, 2008) ou até mesmo

envolvimento com transgressões legais (Parsons & Bynner, 2005). A alta prevalência e os impactos na vida dos indivíduos nos alertam que o transtorno tem uma relevância em termos de saúde pública e também que sua melhor elucidação deve ser alvo de investigação de cientistas de áreas da saúde e educação.

A discalculia tem uma origem neurobiológica e as dificuldades associadas ao quadro permanecem por toda a vida (Butterworth et al., 2015). Uma revisão sistemática de estudos longitudinais de indivíduos com dificuldades na matemática (Nelson & Powell, 2017) identificou que, em todos os trabalhos selecionados, as crianças com problemas na aprendizagem melhoraram o desempenho na disciplina com o passar do tempo, todavia permaneceram com piores medidas quando comparadas aos pares. Outro ponto levantado pela revisão diz respeito ao critério diagnóstico (Nelson & Powell, 2017). Os autores observaram uma falta de consistência entre os estudos sobre o que é considerado "dificuldade na matemática". Um estudo dentre os 35, considerou o critério de resposta à intervenção, enquanto poucos estudos utilizaram como critério medidas estatisticamente inferiores em momentos diferentes. A maioria dos estudos usou pontos de corte em tarefas matemáticas padronizadas, podendo estes pontos serem mais conservadores (percentil 10) ou liberais (percentil 25) (Nelson & Powell, 2017).

Existem diferentes critérios diagnósticos para os transtornos de aprendizagem, sendo os mais utilizados: a) psicométrico: baseada em um ponto de corte em testes padronizados; b) desempenho: comparação das habilidades acadêmicas da criança ao que seria esperado conforme parâmetros curriculares; c) discrepância entre as medidas de inteligência e desempenho escolar: diferença de pelo menos 1.2 desvios-padrão entre teste padronizados; d) resposta à intervenção: baseado nas taxas de melhora da criança mediante intervenções adequadas ao quadro e mais recentemente e) critérios alternativos: uso metodologias mais experimentais descritas na literatura (Hale et al., 2010; 2016). Os diferentes critérios diagnósticos e, consequentemente, a dificuldade e inconsistência na identificação de crianças com discalculia são problemas discutidos há mais de uma década (Geary, 2015; Mazzocco, 2007) e acabaram por direcionar pesquisas sobre genética, cognição e comportamento acerca da aprendizagem da matemática e suas dificuldades.

A investigação científica sobre a aprendizagem da matemática e da discalculia dentro das neurociências cognitivas é bastante recente e apesar do volume de informações já produzido, os dados identificados nos níveis de análise mais básicos (genéticos,

moleculares, cerebrais) ainda carecem de melhor entendimento. Ademais há lacunas no entendimento de como esses fatores genético-moleculares se associam à aspectos cognitivos e comportamentais e mais ainda, como essas evidências se aplicam à prática clínica. Uma proposta na direção de melhor esclarecer a relação entre a genética e o comportamento, trata do estabelecimento dos endofenótipos, ou seja, fenótipos intermediários, mensuráveis e que podem ser utilizados como marcadores de vulnerabilidade para um determinado transtorno (Waldman, 2005). Conforme supracitado, apesar de bem consolidada as informações sobre o quadro da discalculia do desenvolvimento, os critérios diagnósticos ainda não estão muito bem operacionalizados ou consistentes. Do ponto de vista cognitivo, diferentes mecanismos têm sido associados com as dificuldades na matemática, ou seja, a discalculia é entendida hoje como um transtorno de heterogeneidade cognitiva (Henik, Rubinsten & Ashkenazi, 2015; Haase et al., 2012).

Um dos primeiros domínios identificados como relevante para aprendizagem da matemática foi a memória operacional, sendo sua importância bem estabelecida, tanto no que se refere ao desenvolvimento típico quanto às dificuldades (Raghubar et al., 2010). Memória operacional diz respeito à capacidade cognitiva limitada que permite o armazenamento e processamento temporário de informações (Baddeley, 2012). Os estudos nessa área investigam de maneira mais destacada, como os componentes de memória operacional associam-se às diferentes habilidades aritmética (Van de Weijer-Bergsma, Kroesbergen, Van Luit, 2014). No início da aprendizagem a manipulação visuoespacial das informações é mais importante para o desempenho, no entanto, com o passar dos anos os componentes verbais passam a exercer um papel de maior proeminência (McKenzie, Bull & Gray, 2003; Simmons, Willis & Adams, 2012). Adicionalmente um trabalho recente indicou que tarefas que avaliam componentes espaciais da memória operacional foram capazes de discriminar grupos de crianças com problemas na aprendizagem da matemática (Mammarella et al., 2017). Cabe destacar que algumas habilidades aritméticas são mais dependentes da memória operacional, tais como: contagem, transcodificação e cálculos (Raghubar et al., 2010). Além disso, tem-se que para a maioria das habilidades adquiridas, quanto maior a proficiência, menor a demanda por memória operacional.

O processamento fonológico é primariamente associado às habilidades de leitura e escrita. Entretanto, diferentes evidências mostram que esse é um dos principais elos entre a aprendizagem da matemática e da leitura, podendo ser, inclusive, o marcador cognitivo que explica a alta comorbidade entre dislexia (Transtorno Específico de Aprendizagem com

prejuízo na leitura) e discalculia (Lopes-Silva et al., 2015). Uma vez que entendemos o processo de leitura de palavras como uma decodificação dos símbolos (grafemas) em sons (fonemas), podemos supor que o processamento fonológico se associa à aprendizagem da aritmética e processamento numérico, em especial nos aspectos simbólicos, como por exemplo a transcodificação numérica verbal-arábica (Lopes-Silva et al., 2014; 2016) e a multiplicação (Grabner et al., 2009). Recentemente, um estudo identificou que habilidades de consciência fonológica (mensurada por uma tarefa de supressão de fonemas) é importante para o desempenho de crianças em tarefas de leitura e escrita de números (Lopes-Silva et al. 2016). Adicionalmente, De Smedt, Taylor, Archibald e Ansari (2010) demonstraram que a consciência fonêmica é preditiva da capacidade de resolução de operações aritméticas simples, mas não de operações mais complexas. A explicação para isto é que as computações simples, como fatos aritméticos, são armazenadas verbalmente na memória de longo prazo, exigindo, portanto, a atuação do processamento fonológico (Dehaene, 1992, vide revisão por Haase, Costa, Antunes, Alves, 2012).

Além das habilidades de memória operacional e processamento fonológico, outros domínios gerais, como habilidades visoespaciais e funções executivas, já foram implicados com a aprendizagem da matemática e a discalculia. Além disso, há o domínio cognitivo específico da aprendizagem da matemática: o senso numérico. As habilidades do senso numérico são inatas, aproximadas e seguem leis psicofísicas (Dehaene, 1997). Assim como as outras habilidades cognitivas, o senso numérico tem uma distribuição normal na população (Halberda et al., 2012). Essa variabilidade nas habilidades do senso numérico tem sido associada a diferenças no desempenho matemático em crianças e adultos (Chen & Li, 2014). Em um dos primeiros e mais influentes estudos, Halberda, Mazzocco e Feigenson (2008) demonstraram que a fração de Weber de adolescentes de 14 anos era inversamente proporcional ao desempenho aritmético em dois testes de desempenho matemáticos padronizados. Ou seja, quanto melhor as habilidades de senso numérico, melhor o desempenho escolar em matemática. Ademais, Fazio, Baile, Thompson & Siegler (2014) demonstraram que após controlar habilidades de domínios cognitivos gerais, o conhecimento numérico simbólico e não simbólico (senso numérico) contribuíram de maneira independente para o desempenho aritmética.

Evidências que corroboram a relação entre senso numérico e desempenho aritmético advêm da investigação em crianças com discalculia do desenvolvimento. Diversos estudos demonstraram que uma baixa acuidade numérica em tarefas de comparação de pontos

(senso numérico) é encontrada em crianças com dificuldade de aprendizagem da matemática (Pinheiro-Chagas et al., 2014, Mazzocco, Feigenson & Halberda 2011, Piazza et al., 2010). Outrossim, um estudo mostrou que crianças com 1.5 desvios padrões abaixo da média no teste brasileiro de Desempenho Escolar da Matemática (TDE – Stein, 1994) apresentaram fração de Weber estatisticamente pior que seus pares mesmo após controle da comparação por inteligência dos grupos (Costa et al., 2011). Adicionalmente, observamos que déficits nas medidas de senso numérico mostraram-se estáveis e inferiores ao longo de um programa de intervenção em uma paciente com o diagnóstico de discalculia do desenvolvimento (Júlio-Costa et al., 2015). Todavia, este déficit em crianças com discalculia ainda é controverso (Nöel & Roussele, 2011, Fazio et al., 2014).

Além das questões cognitivas, aspectos emocionais se associam a aprendizagem da matemática e a discalculia. A ansiedade matemática é uma fobia específica que envolve um sentimento de tensão e desesperança eliciado por estímulos ou situações matemáticas (Chinn, 2009). Assim com as outras fobias específicas a ansiedade matemática se associa a respostas emocionais, cognitivas, afetivas, psicofisiológicas e comportamentais (Haase, Guimarães & Wood, in press). A relação entre ansiedade matemática e desempenho matemático é bidirecionada (Haase et al., in press; Júlio-Costa, Lima & Hasse, 2015). Resumidamente, os conhecimentos atuais nos indicam que altos níveis de ansiedade matemática consomem recursos cognitivos que deveriam ser destinados a resolução das tarefas matemáticas (Dowker, Sarkar & Looi, 2016). Por outro lado, um baixo desempenho matemático recorrente leva a aversão dos estímulos de mesma natureza (Dowker et al., 2016). Considerando essa relação, observa-se que crianças com discalculia apresentam níveis mais altos de ansiedade matemática podendo esta característica prejudicar ainda mais o desempenho (Dowker et al., 2016; Hill et al., 2016; Rubinsten & Tannock, 2010).

Pode-se entender cada uma das características descritas até aqui como um endofenótipo da discalculia. As habilidades cognitivas e emocionais são aspectos mais apurados e mensuráveis que o desempenho matemático que depende não só das funções mentais, mas também da interação com todas as questões ambientais. Desta maneira, averiguar associações entre os endofenótipos e aspectos genéticos é uma estratégia investigação mais refinada para o entendimento das influências individuais na aprendizagem da matemática e da discalculia do desenvolvimento.

O conhecimento sobre genética da discalculia proporcionalmente é menor que de outros transtornos do neurodesenvolvimento, mas existe. O próprio diagnóstico da discalculia é corroborado através de pesquisas com gêmeos que apontam para a etiologia multifatorial do desempenho na matemática, com distribuição contínua na população (Petrill et al., 2012; Willcutt et al., 2010). Além disso, o risco de se ter uma segunda criança com discalculia em uma família é maior de 5 a 10 vezes em relação a população geral (Monuteaux et al., 2005). A herdabilidade estimada da discalculia em estudos de genética comportamental apontam para valores maiores que 60% (Kovas et al., 2007; 2009).

Outras evidências das questões genéticas na discalculia do desenvolvimento emergem do estudo das síndromes genéticas. Síndromes como Turner, Velocardiofacial, X-frágil apresentam um fenótipo comportamental (ou seja, um padrão de comportamento sindrômico) de dificuldades de aprendizagem na matemática (Mazzocco, 2015). Como as síndromes têm origens conhecidas do ponto de vista genético, entende-se que os fenótipos expressos por esses indivíduos se associam as alterações biológicas identificadas.

Influências genéticas sobre a aprendizagem da matemática em indivíduos com alterações no cromossomo 22 foram evidenciadas (Carvalho et al., 2014; Oliveira et al., 2014). Mais especificamente, identificou-se associação de um polimorfismo do gene da enzima catecol-orto-metiltransferase na posição 158 (COMT val158met), encontrado também no cromossomo 22 (Júlio-Costa et al., 2013). Observou-se que indivíduos com pelo menos um alelo de metionina (met) apresentaram melhor desempenho em uma tarefa de senso numérico e em tarefa de transcodificação numérica que demanda entre outras habilidades, a memória operacional. Outros estudos já demonstraram a influência do polimorfismo COMT val158met no desempenho de tarefas numéricas (Herman et al., 2013; Tan et al., 2007). Ademais há associações consistentes estabelecidas entre o polimorfismo da COMT val158met e a ansiedade (Gottschalk & Domschke, 2017; Mier et al., 2010) e quadros de ansiedades específicas como fobia social (Furmark, 2009), fazendo-se necessária a investigação da associação desse polimorfismo com a ansiedade matemática.

A COMT é uma enzima que participa do metabolismo da dopamina, tendo um papel relevante principalmente em regiões pré-frontais (Chen et al., 2004). Ativação de regiões frontais associam-se com o desempenho em tarefas executivas, incluindo tarefas que demandam memória operacional (Dickinson and Elvevåg, 2009), um dos endofenótipos da discalculia. Além da COMT, o metabolismo da dopamina envolve a participação de

transportador de dopamina (DAT) que também tem sua ação influenciada por variações genéticas (repetições de alelos, p. ex.). Assim a continuidade da investigação da relação de aspectos genéticos associados à dopamina e das habilidades cognitivas subjacentes à aprendizagem da matemática, se contextualiza na busca de melhor elucidação das influências genética na discalculia do desenvolvimento (fenótipo). O caminho a percorrer ainda é longo, todavia acredita-se que a presente tese possa colaborar na exposição de evidências em diferentes níveis de análise (genético e cognitivo, principalmente) na área de pesquisa da cognição numérica.

1.1. Estrutura da dissertação

Seguindo as recomendações do Programa de Pós-graduação em Neurociências da UFMG, esta tese será apresentada em formato de artigos científicos com três estudos experimentais:

-O primeiro artigo, intitulado *The role of intelligence in characterizing the profile of children with Math learning difficulties"*, apresenta uma discussão sobre os critérios diagnósticos da discalculia. Mais especificamente objetivou-se investigar a relevância da inteligência na identificação de crianças de 7 a 12 anos com dificuldades na matemática e, consequentemente, a utilidade do critério da discrepância.

-O segundo artigo, intitulado ***"****COMT Val158Met and DAT1- 3'- UTR VNTR interfere with working memory performance of scholar children in Brazil*". O objetivo do estudo foi investigar a influência dos genes da COMT e DAT1, envolvimentos na via dopaminérgica, no desempenho de tarefas de memória operacional e aritmética em crianças de 7 a 12 anos. Foram testados diferentes modelos genéticos de dominância, codominância e heterose. Cabe ressaltar que a memória operacional é dos endofenótipos mais relevantes para aprendizagem da matemática.

-O terceiro artigo, intitulado *"How is math scary for boys and girls? Math anxiety associated with sex by COMT val158met polymorphism"* teve por objetivo investigar possíveis influências do polimorfismo da COMT, considerando diferenças de sexos, na ansiedade matemática de crianças de 7 a 12 anos.

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2. Objetivos

2.1. Objetivo Geral

A presente tese investiga acerca dos critérios de identificação de crianças com dificuldades na matemática, em especial o critério da discrepância. Objetiva-se averiguar o papel da inteligência na discriminação de alunos com e sem dificuldade nessa disciplina. Além disso, objetiva-se também pesquisar a influência de aspectos genético-moleculares das vias dopaminérgicas sobre os mecanismos cognitivos subjacentes a aprendizagem da matemática e consequentemente suas dificuldades.

2.2. Objetivos Específicos

(a) Investigar o papel da inteligência na discriminação de crianças com dificuldade de aprendizagem na matemática, com o intuito de levantar evidências em relação ao critério diagnóstico da discrepância para os transtornos de aprendizagem;
(b) Averiguar diferenças no perfil cognitivo entre crianças com dificuldades na matemática com i) inteligência discrepante e ii) inteligência não-discrepante;
(c) Investigar a possível associação da biodisponibilidade de dopamina, operacionalizada por variações genéticas individuais identificados nos genes da COMT e do DAT1, no desempenho de crianças de 7 a 12 anos em tarefas de memória operacional e aritmética;
(d) Pesquisar se há interação entre os genes da COMT e DAT1, sexo e desempenho em tarefas de memória operacional em crianças de idade escola
(e) Averiguar existência de diferença entre os genótipos da COMT (rs4680) em relação ao desempenho matemático e à fatores emocionais da aprendizagem na matemática (ansiedade matemática) considerando possíveis influências do sexo em crianças de 7 a 12 anos.

3. The role of intelligence in characterizing the profile of children with Math learning difficulties

Annelise Júlio-Costa[1], Isabella Starling-Alves[2],
Andressa Moreira Antunes[3] e Vitor Geraldi Haase[4]

1. Programa de Pós-graduação em Neurociências, Instituto de Ciências Biológicas, Universidade Federal de Minas Gerais (UFMG), Brazil
2. Department of Educational Psychology, University of Wisconsin Madison, USA
3. Neuroscience Ilumina Institute, Minas Gerais, Brazil
4. Department of Psychology, Graduate Program in Children's and Adolescents Health, Graduate Program in Psychology: Cognition and Behavior, Graduate Program in Neuroscience, Universidade Federal de Minas Gerais (UFMG), Instituto Nacional de Ciência e Tecnologia sobre Cognição, Comportamento e Ensino (INCT-ECCE)

ABSTRACT: Learning disabilities have an impact on one's life academically speaking, but also concerning its emotional and social aspects. Despite the increase in the volume of research, much is questioned about the diagnostic criteria, especially on the difficulties of Mathematics, which are less studied than reading difficulties. The criterion of discrepancy proposes that children who present a significant difference between school achievement and intelligence should be diagnosed. Thus, the aim was to investigate differences in the cognitive profile of children with Math learning difficulties and discrepant intelligence, and also children with Math learning difficulties and low intelligence. Results showed that intelligence was not relevant to discriminate groups of children with or without Math difficulties. Besides, intelligence levels impacted only global cognitive measures, not numerical abilities cognition. Data supports an argument that questions the real utility of the criterion of discrepancy. This argument leads us to do the first study that investigated such hypothesis: how the learning difficulties in Mathematics relate to several cognitive global and numerical abilities. The fragility of the criterion of discrepancy does not lie in the validity of intelligence as a construct. Although its use in the diagnosis was controversial, intelligence was relevant in the comparative profile of children with learning difficulties, also presenting a direct relation with the severity level of these deficits.

3.1. Introduction

We live in a world with increasing cognitive demands for individuals. To succeed, a high level of education, and proficiency in writing, reading, and Math skills are needed. Although academic performance depends on the quality of resources (quality of education, for example), it is mainly influenced by individual differences (Asbury & Plomin, 2013).

Specific Learning Disorders are defined as a heterogeneous group of disabilities manifested by significant and persistent difficulties in the acquisition and application of reading, writing and mathematical reasoning (Pennington, 2008). Such difficulties cannot be attributed to global cognitive deficits, neurological lesions, sensory or motor problems, or poor teaching quality. According to Pennington (2008), the prevalence of learning disorders is 5-15% in school-aged children. As proposed by the medical nosology described in the manuals (APA, 2013, WHO, 1992), the diagnosis is categorical and defined from arbitrary cut-off points. Individuals with learning disorders do not present genetic, cognitive, nor behavioral characteristics that are qualitatively different when compared to the rest of the population (Kovas & Plomin, 2006; Asbury & Plomin, 2013).

Developmental dyslexia is the specific learning disorder of reading. Cognitively, individuals diagnosed as dyslexic present deficits related to phonological processing (mainly phonological awareness), verbal working memory, and lexical retrieval (Galaburda, LoTurco, Ramus, Fitch & Rosen, 2006; Ramus & Szenkovits, 2008). From the cerebral point of view, there is a progressive increase of activation in the frontal areas, functioning as a compensatory mechanism of sub-activation in posterior regions and confirming the phonological nature of the deficits (Shaywitz & Shaywitz, 2005; Shaywitz, 2006).

On the other hand, developmental dyscalculia, which is the main target of the present study, is a specific disorder in learning Mathematics. Children diagnosed with this disorder present difficulties in manipulating quantities, automating arithmetic facts, and executing procedures, as well as difficulty in understanding mathematical reasonings (Kucian & von Aster, 2015). The neural patterns in children with dyscalculia are associated with reduced activation in intraparietal regions of the brain, and increased in frontal regions (Kaufmann, Wood, Rubinsten & Henik, 2011). The cognitive difficulties associated with dyscalculia are less studied than those of dyslexia, and might be associated with deficits in both general and specific areas.

The specific domain of numerical cognition, the number sense, is defined as the ability to represent and manipulate non-symbolic magnitudes (Dehaene, 1997). Number sense skills are innate, approximate, and described by psychophysical laws (Dehaene, 1997), such as Weber's Law. Such capability is measured by the Weber fraction, a constant that provides an estimate of the minimally perceptible numerical difference, and the resolution capability of the underlying system (the number sense acuity; Dehaene, 2007). These skills have been associated with the variability of mathematical performance in children and adults (Halberda, Mazzocco & Feigenson, 2008, Chen & Li, 2014; Fazio, Baile, Thompson & Siegler, 2014), and individuals with mathematical learning difficulties might exhibit an altered Weber fraction when compared to their peers (Piazza et al., 2010, Mazzocco, Feigenson & Halberda, 2011, Costa et al., 2011, Haase et al., 2014; Pinheiro-Chagas et al., 2014; Júlio-Costa et al., 2015; Budgen & Ansari, 2016).

The general domains associated with deficits in individuals with Math learning difficulties are working memory (WM), phonological processing, and visuospatial skills (Haase et al., 2012). The importance of working memory for math learning has been well established. Geary (1993, 2006) proposed that one's phonological memory storage capacity is associated to his acquisition and consolidation of arithmetic facts. Likewise, it was found that in tasks related to number transcoding (the ability to switch from one numerical notation to another, e.g. (2 --> two --> **), children with greater WM span presented superior performance in comparison to their peers with smaller WM span (Camos, 2008). Task performance also correlates with the complexity of the items to be transcoded. From the developmental point of view, at the beginning of the learning process, one's visuospatial manipulation of the information is pointed the most important for the performance. However, over the years, verbal components of WM have become more prominent (McKenzie, Bull & Gray, 2003; Raghubar, Barnes & Hecht, 2010; Simmons, Willis & Adams, 2012; Van de Weijer-Bergsma, Kroesbergen, Van Luit, 2014). Additionally, some mathematical skills are more dependent on WM, such as counting, transcoding, and complex calculations (Raghubar et al., 2010; Lopes-Silva et al., 2014, 2016), since they involve direct manipulation of information.

Deficits in components of phonological processing (phonological awareness, phonological memory, and lexical retrieval) are primarily associated with reading and writing learning difficulties. However, recent studies have shown that these deficits are one of the main links between the learning of Math and reading, and might even be a cognitive marker that

explains the high comorbidity between dyslexia and dyscalculia (Lopes-Silva et al., 2014; 2016). Phonological processing is associated with arithmetic and numerical learning, especially in symbolic aspects such as verbal-arabic numerical transcoding (Lopes-Silva et al., 2014; 2016) and multiplication (Grabner et al., 2009). De Smedt, Taylor, Archibald, and Ansari (2010) have demonstrated that phonemic awareness is predictive of the ability to solve simple arithmetic operations, rather than more complex ones.

Finally, deficits in visuospatial skills have also been associated to math difficulties. Important evidences have emerged from patients with right hemisphere lesions (Grana, Hofer & Semenza, 2005) and studies regarding nonverbal learning disabilities, which are characterized by both visuospatial and Math learning deficits (Rourke, 1989; Mammarella & Cornoldi, 2014). In this sense, there are several studies showing that a considerable group of children with Math learning difficulties present weak visuospatial processing (for review Mammarella, Caviola, Giofrè, Szücs, 2017).

Despite of the progress of research on specific learning disorders, there is a controversy surrounding a theme that has direct clinical implications: the diagnostic criteria. Any diagnosis involves clinical and historical (genetic and environmental) characteristics of individuals, especially in learning disorders that do not have biological markers. School achievement presents a Gaussian distribution in the population (Asbury & Plomin, 2013), which means that the lowest portion of individuals reaches arbitrary criteria and receive the diagnosis of learning disorder (Hale et al., 2010; 2016).

One such arbitrary criterion is the psychometric, that proposes that the diagnosis should be based on the child's score on a test of school achievement (reading, writing, and Math). Those individuals with scores below the 10th percentile, who do not reach the exclusion criteria (intellectual disability, history of pedagogical inadequacy, neurological lesions, and sensory-motor or emotional deficits), fit into a Specific Learning Disorder diagnosis that can be coded such as dyslexia, dyscalculia, or both, according the type of deficit observed (Sternberg & Grigorenko, 2002; Mazzocco, 2007, Pennington, 2008). The cutoff point determination is arbitrary, associated to the frequency of the population scores (Asbury & Plomin, 2013), and it is corroborated by studies on the cognitive profile of participants presenting all scores ranges in performance tests. Another possibility is the criterion of discrepancy between Intellectual Quotient (IQ) and school achievement (Sternberg &

Grigorenko, 2002). By definition, Specific Learning Disorders refer to persistent, lower than expected school performance, based on the overall intellectual functioning.

Intelligence is the most validated, and therefore the most robust, construct in psychology (Deary & Johnson, 2010; Hunt, 2011). This is the main isolated predictor of academic performance and psychosocial and health outcomes throughout life (Deary & Johnson, 2010, Strenze, 2007). Correlations between intelligence and school achievement are around 0.5 when both constructs are measured simultaneously (Asbury & Plomin, 2013), whereas the ability of IQ to predict future school performance is based on correlations of up to .8 or greater (Deary & Johnson, 2010). However, one problem in the studies about the influence of intelligence on school learning is the heterogeneity of global cognitive functioning measures. Through dynamic models of repeated measures of intelligence from childhood to adulthood, Ferrer & McArdle (2004) have shown that the relationship between fluid and crystallized intelligence and academic performance varies over time, with fluid intelligence having the greatest impact on learning. In this sense, it is important to remember that IQ measurements involve aspects of these two types of intelligence. In addition, factorial analysis revealed that there is a distinction between crystallized and fluid measures of intelligence, from the point of view of neural activation (Duncan et al., 2000), and patterns of association with other cognitive measures, indicating that fluid intelligence is strongly correlated to measurements of working memory (Conway et al., 2002).

The validity of the criterion of discrepancy, which uses IQ for diagnosis, has been strongly questioned in the academic community over the last few decades (Sternberg & Grigorenko, 2002, Stanovich, 2005, Restori, Katz & Lee, 2009). The team of specialists who produced the current version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V, APA, 2013) has even removed the need for this criterion, which until 2013 was required (APA, 2000).

The relationship between intelligence and learning to read, including dyslexia, has been extensively studied, and there are several arguments supporting the criterion of discrepancy as well as arguments invalidating it. An argument favorable to the discrepancy criterion is that, at the genetic level, it is possible that the heritability of dyslexia is higher in individuals with high intelligence ($h^2 = 0.75$) than in individuals with low intelligence ($h^2 = 0.50$) (Wadsworth, Olson & DeFries, 2010). Cognitive evidence from a longitudinal study with annual measures of different groups of children and adolescents (typical readers,

compensated dyslexics and dyslexics) have shown, through the use of dynamic statistical models, that there is a coupling between reading and intelligence skills for typical readers (Ferrer, Shaywitz, Holahan, Marchione & Shaywitz, 2010). The same does not occur for dyslexics, and in these individuals there is an uncoupling between the two variables. In both cases, coupling or uncoupling is progressive and, for children with dyslexia, intelligence does not play a significant role on the promotion of reading, neither does it increase cognitive development. These results corroborate the criterion of discrepancy and have clinical implications, although this kind of clinical evidence requires years of repeated assessments.

Another evidence in favor of IQ-reading discrepancy is that, although intelligence accounts for only a small fraction of variance in learning isolated words, its effects are independent of phonemic awareness (Shantil & Share, 2003; Christopher et al., 2012). In a recent study, when intelligence was inserted in a regression model that had a single-word reading task as a dependent variable, only phonemic awareness tasks remained in the model (Lopes-Silva et al., 2016), which is considered to be the cognitive marker for dyslexia (Ramus et al., 2003). On the other hand, intelligence plays a crucial role in understanding text (Shantil & Share, 2003; Christopher et al., 2012), and it is not only important for diagnosis, but also for dyslexia rehabilitation programs.

In the preparation of the current version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5, APA, 2013), as a result of a long debate, many researchers have indicated that the criterion of discrepancy is not valid for dyslexia (Klesczewski et al., 2015; van Bergen et al., 2014; Ehlert, Scheroeders & Fritz-Stratmann, 2012). The first argument against this criterion is that cognitive mechanisms in reading disorder are independent of IQ. A meta-analysis investigated cognitive differences between children with developmental dyslexia and children with poor reading performance and low intelligence (Hoskyn & Swanson, 2000). Children with dyslexia presented better performance in several measurements (e.g. lexical knowledge and visuospatial processing), but both groups presented similar performance regarding phonological processing. In addition, regression models have shown that phonological difficulties are the deficits common to both groups, regardless of intelligence, which was significantly higher in the dyslexic group (Hoskyn & Swanson, 2000).

Gathering data from several studies, Gresham and Vellutino (2010) have identified that IQ is not a strong predictor of word reading, nor of the intervention success for individuals with

dyslexia, as also shown by meta-analysis (Stuebing et al., 2009). Authors have suggested that such findings are relevant, and ruled out the criterion of discrepancy. In addition, the findings of Shantil & Share (2003), cited above, point out that general cognitive measures explain only a small part of single-word reading abilities, but almost half of the reading comprehension, supporting the data of Gresham and Vellutino (2010) and Stuebing et al. (2009).

Regarding cerebral evidences, Tanaka and colleagues (2011), using the functional magnetic resonance method, have found that two independent groups of children with reading difficulties, discrepant and non-discrepant, had a similar pattern of brain activation. Both groups exhibited reduced activation in parietotemporal regions of the left hemisphere, which are associated with phonological processing (Tanaka et al., 2011). Considering as dyslexic only children with the intelligence-reading discrepancy would let the group of individuals with lower intelligence, who demand more support, without a proper diagnosis and treatment (Sternberg & Grigorenko, 2002; Restori, Katz & Lee, 2009; Hale et al., 2010, 2016).

Dennis and colleagues (2009) have discussed the problem of using intelligence in studies of developmental disorders, such as learning disorders. According to the authors, when using intelligence measures as a covariate, for example, the effects would be masked, since this variable correlated in some levels with several outcomes. The commonality between intelligence and school performance can lead to statistical distortions caused by regression to the mean (Dennis et al., 2009), which results in an inflation of diagnostic rates (false positives) in children with higher intelligence. On the other hand, in children with lower intelligence, the risk of false negative diagnoses increases. However, this critique does not take into account the fact that intelligence is a complex construct, composed by distinct factors differently correlated to school achievement (Deary & Johnson, 2010). A review of the literature on reading learning difficulties suggests that vocabulary measures are less relevant for reading isolated words than measures of nonverbal intellectual abilities associated to fluid intelligence (Deary et al., 2007; & Johnson, 2010).

Regarding dyscalculia, specifically, the construction of arguments against or in favor of the criterion of discrepancy is still incipient. A longitudinal, pioneering study by Mazzocco and Myers (2003) found that a maximum of 20% of the children classified as dyscalculics from the preschool to the third year were overlapped, considering the two diagnostic criteria used: being below the 10th percentile in Math tests standardized, and the discrepancy between

intelligence and Math achievement. Interestingly, these authors still identified that children with persistent difficulties in Mathematics had a higher frequency of reading disorder in the four assessments taken, compared to other children. Ehlert, Scheroeders & Fritz-Stratmann (2012) criticized the discrepancy criterion for dyscalculia by revealing that two groups of children with Mathematical difficulties, with and without discrepancy, presented similar performance in the six mathematical competences evaluated by the TEMA-2 test (knowledge quantity comparison, numerical comparison, numerical knowledge, domain of facts, calculations, and mathematical concepts).

The evidences are fragmented, but the validity of the discrepancy criterion for Math disorder has not been properly tested. The learning of Mathematics is complex, and it depends on general and specific mechanisms. Brankaer, Ghesquière & De Smedt (2014) have showed that the ability of processing symbolic and non-symbolic magnitudes (number sense) was similar in two groups of 7- and 8-year-old children: one was a discrepant group in mathematical performance and intelligence, and the other was non-discrepant. In addition, both groups were inferior to the control group regarding Math measures. Considering those groups differences in intelligence measurements (Raven) and working memory, the authors argued that basic numerical skills are independent of intelligence (Brankaer, Ghesquière & De Smedt, 2014).

The same type of evidence emerged from studies with individuals with genetic syndromes associated with learning disabilities in Mathematics, and intellectual disability, such as the Velocardiofacial Syndrome (De Smedt, Swillen, Verschaffel, & Ghesquiere, 2009; Simon et al., 2008) and Williams syndrome (O'Hearn & Landau, 2007). One study compared the number sense skills (operationalized by the Weber fraction) of a group of typical children, a group of children with intellectual disability, and a group of children with Velocardiofacial Syndrome (Oliveira et al., 2012). The results showed that children with reduced intelligence presented a Weber fraction statistically similar to those of typical children, and superior than children with Velocardiofacial syndrome.

In general, the association between intelligence and performance in Mathematics seems to be restricted to numerical skills that are hierarchically superior to the number sense in the learning process. Geary, Hoard and Nugent (2012), in a longitudinal study with 275 children, identified that intelligence contributed independently to the resolution of addition calculations, and correlated to more efficient strategies throughout the evaluated school years (1st to 4th).

However, a study with the same sample revealed that it was not possible to identify differences in intelligence between groups of children with Math learning disorder and poor performance in Mathematics (Geary, Hoard, Nugent & Bailey, 2012). The cluster analysis and growth curves (5-year measurements) did not identify to which group the children belong, suggesting the normal distribution of mathematical skills and arbitrary points for the diagnostic criteria. However, it is important to note that children in the group with the disorder presented lower scores in tasks of reading skills since the first assessment (Geary, Hoard, Nugent & Bailey, 2012).

A recent study investigated the predictive power of measurements of nonverbal IQ, vocabulary, phonemic awareness, lexical rescue, and verbal working memory on mathematical performance. Predictors were measured seven months before the endpoints, which included the problems of the Woodcock-Johnson-III battery and the Research-based Early Math Assessment battery in preschool children (Foster, Anthony, Clements & Sarama, 2015). The results showed that phonemic awareness and nonverbal IQ were the only predictors isolated from mathematical performance, even when the initial measures of numerical abilities were controlled.

In another research using trajectory analysis, the fluid intelligence (measured by Raven) was also isolated predictor of arithmetic performance and number line estimation a year later (Hornung, Schiltz, Brunner & Martin, 2014). This study was performed in preschoolers. The same type of longitudinal evidence has been demonstrated by other authors (Passolunghi, Cargnelutti & Pastore, 2014; Ren, Schweizer, Wang & Xu, 2015). What makes it difficult to understand the findings as a whole are the variety of mathematical and intelligence measurements and, consequently, the variation of the cognitive mechanisms involved in the tasks.

Although the theoretical framework on learning disorder in Mathematics is not as broad as that of reading, it is possible to expect a similar pattern of functioning for the two disorders, based on the data available in literature. For example: intelligence has little influence on the most basic learning abilities that would depend on specific domains (phonemic awareness / number sense). However, the IQ level would be important for performing more complex tasks, such as text comprehension and calculations. The generalist hypothesis (Plomin & Kovas, 2005; Kovas et al., 2007; 2009) also provides insights for understanding the close relationship between mathematical and reading performance. Through genetic behavior

methodologies, there is in the literature that the genes which influence mathematical abilities are basically the same ones that influence the areas of language (Kovas et al., 2007). The idea is that the same genes affect a range of abilities, including scholastic performance and intelligence (pleiotropy effect), however the specializations of deficits would occur through interaction with the environment (Kovas et al., 2007; Trzaskowski, Shakeshaft & Plomin, 2013), and can expect that children with multiple deficits would be those with a worse genetic background. In addition, there is a high rate of comorbidity between the two disorders (Pennington, 2008), despite the specific cognitive deficits of each of them (Landerl, Fussenegger, Moll & Willburger, 2009).

Investigations of learning disabilities have increased considerably. However, there is no consensus between clinics and research experts regarding diagnosis criteria. The discrepancy criterion is the most contradictory one. Thus, this study investigated differences in the cognitive profile between children with Math learning difficulties and discrepant intelligence, and children with Math learning difficulties with low intelligence. Both groups are compared to children with typical development. If the discrepancy criterion is relevant, differences between typical development children and children in the discrepant group are expected to be stronger than differences between typical development children and children in the non-discrepant group. Moreover, if the discrepancy criterion is appropriate, it is expected that the non-discrepant group presents better performance than the discrepant group.

3.2. Methods

3.2.1. Participants

Students from 2nd to 7th grades of public and private elementary schools of Belo Horizonte, Brazil, were invited to take part in this study. Children whose parents signed the consent form were presented with a battery of neuropsychological assessment. The initial sample group was composed of 308 children. Seventy-six children were excluded from this group due to reading difficulties, measured through the Brazilian School Achievement Test (z scores < -0.67 PR25). The final sample group was composed by 232 children. No child presented psychiatric or neurologic disorders symptoms. Besides, all children presented intelligence above the 5th percentile in Raven's Coloured Progressive Matrices test. This study was approved by the local IRB (COEP-UFMG).

For analysis, participants were split in groups according to their scores in the Brazilian School Achievement Test (Teste de Desempenho Escolar, TDE, Stein, 1994) and in the intelligence test (Raven's Coloured Progressive Matrices test). Initially, children were split in two groups: Math learning difficulties, and a control group One hundred and ninety-five children with z-scores above -0.67 (PR25) in arithmetic and reading subtests of TDE were assigned to the control group or typical achievement (TA). Thirty-seven children that presented z-scores under -0.67 (PR25) in arithmetic subtest, and above -0.67 (PR25) in reading subtest, were assigned to Math Learning Difficulties group (MLD).

Later on, in order to investigate the influence of intelligence in the profile of children with MLD, this group was split into children with discrepant and non-discrepant Math achievement and intelligence scores. It was calculated a z-score to Raven (intelligence) by age and according to the Manual's norms and a z-score to TDE - arithmetic subtest by grade according norms of Ferreira-Oliveira et al. (2012). To each child, these two z-score were compared. Values equal or above 1.2 standard-deviations were considered discrepant, when intelligence and Math achievement scores were compared. This method was based on criteria of standard diagnosis sets (ICD-10, WHO, 1992) and Klesczwski et al. (2015). Twenty-three children presented z scores below -0.67 (PR25) in the arithmetic subtest, and above -0.67 (PR25) in the reading test, and presented a difference below 1.2 standard-deviations between intelligence and Math achievement as well. Thus, they were classified as MLD-non-discrepant, hereinafter MLD-nondis. Finally, fourteen children were classified as MLD-discrepant (MLD-dis), since they showed achievement below z score -0.67 (PR 25) in arithmetics, and above -0.67 (PR25) in reading, and a difference equal or greater than 1.2 standard-deviations between Math achievement and intelligence. Standard scores (z-scores) were calculated according to the norms for the Brazilian population (Oliveira-Ferreira et al., 2012 e Angelini et al., 1999).

Some data from computerized tasks were corrupted, and it was not possible to analyze them. Data from 14 children were lost in the simple reaction time task. In the nonsymbolic magnitudes estimation task, 11 children were from TA, two from MLD-nondis and one from MLD-dis. In the nonsymbolic magnitude comparison task, data from 15 children from GC, five children from MLD-nondis and two from MLD-dis groups were lost. All Weber fraction scores analyzed in the nonsymbolic magnitude comparison task presented adequate R^2 (R^2<.02; Pinheiro-Chagas et al., 2014).

It is important to highlight that children did not present a clinical diagnosis of developmental dyscalculia, and that participants were recruited through a populational strategy. A liberal cut-off point was used to assign the groups (PR 25; Mazzocco, 2007), but we admit that reading and Math achievement is distributed through a continuum in the population (Asbury & Plomin, 2013).

3.2.2. Procedures

Children were evaluated in two phases. In the first phase, children were examined in groups of eight from the same school year. The assessment protocol consisted of: Raven's Coloured Progressive Matrices test (Angelini et al, 1999), Number Writing (Moura et al., 2013), and the arithmetic subtest of the Brazilian School Achievement Test (Stein, 1994). Tasks that assess reading skills, working memory (verbal and visuospatial), numerical cognition, simple reaction time, and visuospatial skills were applied in individual sessions of approximately 60 minutes. All evaluations were conducted at the child's own school in a quiet room.

3.2.3. Instruments

The Brazilian School Achievement Test - TDE (Stein, 1994) - was used as a criterion for stratification of the groups for the analysis. This is the only psychopedagogical test of school performance for elementary school that has been validated for Brazil. This test presents three subtests that evaluate writing, arithmetic, and reading skills. The subtest of arithmetic consists of 38 Math problems of different complexities: three simple questions of Math oral problems and 35 written calculations. The reading subtest consists of reading (decoding) 70 isolated words, arranged linearly. The terms presented a range from monosyllables to polysyllables. This subtest evaluates the ability to transcode from the grapheme to the phoneme, the mastery of accents, and spelling rules. The writing subtest consists of a dictation of 34 isolated words. This subtest was not included in the current study. The classification of school performance in the TDE is based on the score obtained in each subtest, according to grade. This classification was established based on TDE standardization data from Belo Horizonte, MG (Oliveira-Ferreira et al., 2012). Scores below 25th percentile are considered "inferior" and above 75th percentile “superior”. Scores between 25th and 75th percentile are classified as “average”.

The Raven's Coloured Progressive Matrices test - general intelligence was evaluated through the Raven's Colored Progressive Matrices, validated for Brazilian children (Angelini

et al., 1999). Children with scores below the 5th percentile were excluded from the sample group. Z scores were calculated based on the Brazilian norms (Angelini et al., 1999).

The tasks below correspond to the independent variables of the study:

Rey Complex Figure (copy) - in order to evaluate visuospatial and visuoconstructive abilities, the Rey's complex figure was used. The copy of the figure was punctuated according to the presence, distortion, or absence of the 18 graph-element (Strauss Sherman & Spreen, 2006).

Digit Span (WISC-III) (forward and backward) - the phonological short-term and working memory were evaluated through the span of the forward and backward order of the Digit subtest of WISC (Figueiredo, 2002), which composes the 3rd edition of Brazilian version of the Wechsler Intelligence Scale for Children (WISC III).

Corsi Blocks - visuospatial working memory were evaluated using Corsi Blocks, composed of two conditions: forward and backward order. This test consists of a board with nine blocks that are touched by the examiner in a certain sequence. In the forward condition, the child was instructed to touch the blocks in the same order as the examiner. In the backward condition the child should touch blocks in the reverse order that they were pointed (Kessels et al., 2000).

Simple reaction time - the computerized RT task is a visual detection task used to control for possible differences in basic processing speed, not related to numerical tasks. In this task, the picture of a wolf (height 9.31 cm; length = 11.59 cm) was displayed in the center of a black screen for a maximum time of 3,000 ms. Participants were instructed to press the space bar on the keyboard as fast as possible whenever the wolf appeared. Each trial was terminated with the first key press. The task had 30 experimental trials, with an inter-trial interval varying between 2,000 and 8,000 ms.

The tasks of numerical cognition can be divided according to the type of skill involved. The tasks of numerical processing were operationalized through symbolic (transcoding tasks - Number writing and Number reading) and non-symbolic processing (Non-symbolic magnitude comparison task and Non-symbolic magnitude estimation task). Arithmetic operations were assessed using the Basic Arithmetic Calculations task, and problems orally

formulated through the Arithmetic word problems task. All the tasks of numerical cognition are part of a battery developed by the Laboratory of Developmental Neuropsychology and have already been described in several studies (Costa et al., 2011, Júlio-Costa et al., 2013; Moura et al., 2013, and Lopes-Silva et al., 2014; 2016).

Number Writing (Arabic numerals) - children were instructed to write Arabic numerals dictated orally. The task consists of 40 items, 3 numbers with one digit, 9 numbers with two digits, 10 numbers with three digits, and 18 numbers with four digits. The task was built based on the transcoding model proposed by Barrouillet et al. (2004). The internal consistency of the task is .96 (KR-20 equation). Previous evidence of the validity of this task was obtained by Moura et al., 2013; 2015; Lopes-Silva et al., 2014; 2016.

Number Reading - Twenty-Eight Arabic numbers were printed on a block and presented, one by one, to children, who were instructed to read them aloud. The task has 3 numbers with one digit, 9 numbers with two digits, 8 numbers with three digits and 8 numbers with four digits. The validity of the task was previously demonstrated in Moura et al., 2013 and Júlio-Costa et al., 2013.

Arithmetic word problems - twelve arithmetical word problems were presented to the child on a sheet of paper, while the examiner read them aloud simultaneously to avoid reading proficiency bias. There were six additions and six subtraction items, all of them with single-digit operands with results ranging from 2 to 9 (i.e., "*Annelise has* 9 *cents. She gives* 3 *to Isabella. How many cents does Annelise have now?*"). The child had to solve the problems mentally and write the answer down in Arabic format as quickly as possible, and the examiner registered the time taken for each item. Cronbach's α of this task is .83. Previous evidence of the validity of this task was obtained by Costa et. al. (2011).

Basic arithmetic operations - this task consisted of addition (27 items), subtraction (27 items), and multiplication (28 items) operations for individual application, which were printed on separated sheets of paper. Children were instructed to answer as fast and as accurate as they could, the time limit per block being 1 minute. The arithmetic operations were organized in two levels of complexity, and were presented to children in separated blocks: one consisted of simple arithmetic table facts, and the other of more complex ones. Simple additions were defined as those operations with the results below 10 (i.e., 3 + 5), while complex additions had the results between 11 and 17 (i.e., 9 + 5). Tie problems (i.e., 4 + 4)

were not used for addition. Simple subtraction comprised problems in which the operands were below 10 (i.e., 9 − 6), while for complex subtractions the first operand ranged from 11 to 17 (i.e., 16 − 9). No negative results were included in the subtraction problems. Simple multiplication consisted of operations with results below 25 and with the number 5 as one of the operands (i.e., 2 × 7, 5 × 6), while for the complex multiplication, the result of operands ranged from 24 to 72 (6 × 8). Tie problems were not used for multiplication. Reliability coefficients were high (Cronbach's α > .90). Previous evidence of the validity of this task was obtained by Costa et. al. (2011) and Haase et al. (2014).

Non-symbolic magnitude comparison task - Participants were instructed to compare two simultaneously presented sets of dots, indicating which one contained the larger number. Black dots were presented on a white circle over a black background. On each trial, one of the two white circles contained 32 dots (reference numerosity) and the other one contained 20, 23, 26, 29, 35, 38, 41, or 44 dots. Each magnitude of dot sets was presented eight times. The task comprised 8 learning trials and 64 experimental trials. Perceptual variables were varied in such a way that, in half of the trials, the individual dot size was held constant, while in the other half, the size of the area occupied by the dots was held constant (see exact procedure descriptions in Dehaene, Izard & Piazza, 2005). Maximum stimulus presentation time was 4,000 ms, and inter-trial interval was 700 ms. Before each trial, a fixation point appeared on the screen – a cross, printed in white, with 30 mm in each line. If the child judged that the right circle presented more dots, a predefined key localized in the right side of the keyboard should be pressed with the right hand. In the other case, if the child judged that the left circle contained more dots, then a predefined key on the left side had to be pressed with the left hand.

Non-symbolic magnitude estimation task - Participants were asked to estimate, with a verbal response, the quantity of dots presented on the computer screen. Black dots were presented on a white circle over a black background. Numerosities were 1, 2, 3, 4, 5, 10, 16, 24, 32, 48, 56, or 64 dots. Each numerosity was presented 5 times, each time in a different configuration, and in such a way that the same numerosity never appeared in consecutive trials. The task was comprised of 60 test trials. The maximum stimulus presentation time was 1000 ms, fast enough to avoid counting. The inter-trial interval was 700 ms. As soon as the child answered, the examiner, who was sitting next to the child, pressed the spacebar on the keyboard and typed the child's answer. Between each trial, a fixation point appeared on the screen for 500 ms—a cross, printed in white, with 3 cm in each line. As a measure of non-

symbolic magnitude representation acuity, we calculated the mean coefficient of variation (estimation cv mean) of the numbers ranging from 10 to 64 of the responses for each child (Pinheiro-Chagas et al., 2014). Numbers between 1 and 5 were not included in the analyses because they are on the subitizing range, which require an exact access to non-symbolic magnitude and it is not on the scope of the present work.

3.2.4. Analyses

The statistical analyses were performed in SPSS software, version 20.0. First, we run the drescriptive analyses. Thus, we compared the cognitive profile of typical developmental children (typical achievement group [TA]) with the profile of mathematical learning difficulties (MLD) children. We used the general linear model to investigate possible differences between groups. Afterward, the role of intelligence in the profile of children with MLD was investigated. Individuals with Math difficulties were split into two groups: math achievement-intelligence discrepancy [MLD-dis] and no discrepancy [MLD-nondis]). Later on, these were compared to the typical achievement group. A difference of age was observed between groups. Thus, age was added as covariate to the analysis of variance (ANCOVA). Since multiple comparisons were run, Bonferroni corrections were used to identify statistically significant values. The initials TA, MLD, MLD-dis and MLD-nondis are used across this article to refer to the different groups of children.

3.3. Results

First, the descriptive variables of typical achievement (TA) and MLD children were compared. Groups were matched in sex, age, and grade (Table 1).

Table 1. Demographic characteristic comparison between TA and MLD

		TA	**MLD**	**x^2**	**p**	**w**
		n (%)	**n (%)**			
Sex	Male	78(40)	14(38)	0.67	0.72	0.05
	Female	117 (60)	23(62)			
		Mean (sd)	**Mean (sd)**	**F**	**p**	**η^2**
	Age(month)	121.09(12.1)	121.86(12.8)	0.06	0.95	<.001
	Grade	3.49(1.06)	3.49(1.07)	0.02	0.99	<.001

NOTE: TA=typical achievement; MLD= Math Learning Difficulties; Dis= discrepant

Regarding the cognitive measures, Table 2 shows that TA group presented a performance statistically superior in most measures when compared to MLD. The only exceptions are in the scores of Digit Span and Corsi Blocks in the forward condition (p=0.65, η^2=0.001and p=0.55, η^2=0.002, respectively,) and in the Coefficient of variation-mean (nonsymbolic estimation task) (p=0.165, η^2=0.009).

Table 2. Analysis of variance of the neuropsychological tasks comparing TA and MLD groups

Tasks	TA (n=195)		MLD (n=37)		ANOVA			
	mean	sd	mean	sd	F	df	p	η^2
Raven (z-score)	0.66	0.75	0.17	0.90	12.27	230;1	<.001	0.051
Simple RT	416.72	81.54	446.89	109.50	3.42	215;1	0.066	0.016
Rey Complex Figure(copy)	28.93	5.20	25.38	6.70	13.17	230;1	<.001	0.054
Digit Span (forward)	5.05	0.97	4.97	0.87	0.21	230;1	0.650	0.001
Digit Span (backward)	3.55	0.89	2.95	0.71	15.27	230;1	<.001	0.062
Corsi Blocks (forward)	5.15	0.85	5.05	0.99	0.36	230;1	0.547	0.002
Corsi Blocks (backward)	4.66	1.12	4.22	1.36	4.47	230;1	0.036	0.019
Number writting (percentage)	0.95	0.11	0.84	0.20	21.11	230;1	<.001	0.084
Number reading	27.38	1.44	25.89	2.86	22.64	230;1	<.001	0.090
Simple Addition	11.51	1.34	9.68	3.13	34.55	230;1	<.001	0.131
Complex Addition	11.05	3.65	7.76	4.10	24.24	230;1	<.001	0.095
Simple Subtraction	10.29	2.39	7.65	3.60	31.63	230;1	<.001	0.121
Complex Subtraction	6.79	3.99	4.05	3.79	14.87	230;1	<.001	0.061
Simple Multiplication	10.74	4.91	5.86	5.05	30.44	230;1	<.001	0.117
Complex Multiplication	4.35	4.07	1.19	2.04	21.24	230;1	<.001	0.085
Oral Math Problem	10.29	1.78	7.78	3.44	42.93	230;1	<.001	0.158
Weber Fraction	0.26	0.09	0.30	0.10	7.67	208;1	0.006	0.036
Coefficient of variation (mean)	0.17	0.06	0.19	0.07	1.94	216;1	0.165	0.009

NOTE: TA=typical achievement; MLD= Math Learning Difficulties; Dis= discrepant

Very few studies have investigated the influence of intelligence in the cognitive profile of children with MLD as this study does. In a second block, we run analyses using the MLD group sliptted: MLD-nondis and MLD-dis. The demographic data of TA was similar to both groups with MLD (MLD-nondis and MLD-dis), regarding sex and grade. However, there was a difference in age between groups (p=0.050); the MLD-dis group was younger. This difference presented a moderate size effect (η^2=0.026) (Table 3).

Table 3. Demographic characteristics of TA, MLD-nondis, and MLD-dis comparison

		TA	MLD-Dis	MLD-NDis	x^2	p	w
		n (%)	n (%)	n (%)			
Sex	Male	78(40)	5(36)	9(39)	0.10	0.95	0.001
	Female	117 (60)	9(64)	14(61)			
		Mean (sd)	Mean (sd)	Mean (sd)	F	p	η^2
	Age(month)	121.09(12.1)	115.07(13.9)	126.00(16.0)	3.03	0.05	.026
	Grade	3.49 (1.06)	3.14 (1.10)	3.70 (1.02)	1.18	0.31	.010

NOTE: TA=typical achievement; MLD= Math Learning Difficulties; Dis= discrepant

Table 4 presents group comparison performance in tasks that assessed intelligence, reaction time, working memory, visuospatial skills, and numerical cognition. A general description shows that the MLD-dis group performed similarly to the TA group in the measures of general cognition. Regarding the tasks of numerical cognition, the groups with difficulty in Mathematics performed similarly, while the TA group was statistically superior. We did not find statistical differences in measurements of Simple RT, Digit Span and Corsi Blocks forward, and Coefficient of variation (mean) between the groups.

Regarding the intelligence test (RAVEN), it was noted that the MLD group performed inferiorly than the other two groups that had statistically similar scores considering post-hoc analysis. In addition, the group MLD-nondis was inferior than the group TA in the scores of Digit Span and Corsi Blocks backwards, and also in the copy of Rey Complex Figure. All differences between groups had moderate or strong magnitudes effects (all $\eta^2 > 0.044$) (See Table 4)

Group comparison in numerical cognition tasks revealed that the two groups with difficulty in Mathematics (MLD-nondis and MLD-dis) were statistically similar in most of the measurements, but they were inferior to the TA group in the following: number writing ($\eta^2 = 0.099$), number reading ($\eta^2 = 0.100$), Simple Addition ($\eta^2 = 0.155$), Complex Addition ($\eta^2 = 0.121$), Simple Subtraction ($\eta^2 = 0.138$), Simple Multiplication ($\eta^2 = 0.172$) and Oral Math Problem ($\eta^2 = 0.181$). All these analyses of covariance had a strong magnitude effect. In the Complex Subtraction ($\eta^2 = 0.073$) and Multiplication ($\eta^2 = 0.113$) and in Weber Fraction ($\eta^2 = 0.043$), there was a significant difference between TA and MLD-nondis groups.

Table 4. Analysis of variance of the neuropsychological tasks comparing TA, MLD-nondis and MLD-dis groups

Tasks	TA (n=195)		MLD-Dis (n=14)		MLD-NDis (n=23)		ANCOVA (covariante=age)				Análises de Post-hoc (Bonferroni)
	mean	sd	mean	sd	mean	sd	F	df	p	η²	
Raven (z-score)	0.66	0.75	1.13	0.36	-0.40	0.56	24.21	228;3	<.001	0.175	TA = MLD-Dis > MLD-nondis
Simple RT	416.72	81.54	477.11	134.88	427.26	87.59	2.67	213;3	0.071	0.024	-
Rey Complex Figure(copy)	28.93	5.20	25.29	7.38	25.43	6.40	7.93	228;3	<.001	0.650	TA > MLD-nondis
Digit Span (forward)	5.05	0.97	5.00	1.11	4.96	0.71	0.34	228;3	0.711	0.003	-
Digit Span (backward)	3.55	0.89	3.00	0.55	2.91	0.80	8.13	228;3	<.001	0.067	TA > MLD-nondis
Corsi Blocks (forward)	5.15	0.85	5.07	0.10	5.04	1.02	0.31	228;3	0.733	0.003	-
Corsi Blocks (backward)	4.66	1.12	4.64	1.22	3.96	1.40	5.29	228;3	0.006	0.044	TA > MLD-nondis
Number writting (percentage)	0.95	0.11	0.83	0.23	0.85	0.19	12.50	228;3	<.001	0.099	TA > MLD-Dis = MLD-nondis
Number reading	27.38	1.44	25.71	2.81	26.000	2.95	12.65	228;3	<.001	0.100	TA > MLD-Dis = MLD-nondis
Simple Addition	11.51	1.34	9.79	3.04	9.61	3.24	20.93	228;3	<.001	0.155	TA > MLD-Dis = MLD-nondis
Complex Addition	11.05	3.65	7.00	3.63	8.22	4.37	15.66	228;3	<.001	0.121	TA > MLD-Dis = MLD-nondis
Simple Subtraction	10.29	2.39	7.29	3.64	7.87	3.63	18.18	228;3	<.001	0.138	TA > MLD-Dis = MLD-nondis
Complex Subtraction	6.79	3.99	4.29	3.58	3.91	3.97	8.96	228;3	<.001	0.073	TA > MLD-nondis
Simple Multiplication	10.74	4.91	5.64	5.11	6.00	5.13	23.68	228;3	<.001	0.172	TA > MLD-Dis = MLD-nondis
Complex Multiplication	4.35	4.07	1.36	2.10	1.09	2.04	14.50	228;3	<.001	0.113	TA > MLD-nondis
Oral Math Problem	10.29	1.78	8.43	3.20	7.39	3.59	25.09	228;3	<.001	0.181	TA > MLD-Dis = MLD-nondis
Weber Fraction	0.26	0.09	0.30	0.11	0.31	0.10	4.61	206;3	0.011	0.043	TA > MLD-nondis
Coefficient of variation (mean)	0.17	0.06	0.18	0.08	0.19	0.07	2.20	214;3	0.113	0.020	-

NOTE: TA=typical achievement; MLD= Math Learning Difficulties; Dis= discrepant

If we observe the two group comparisons side by side, it becomes clear that splitting the children with Math difficulties into discrepant and non-discrepant groups did not significantly alter the results. The main results refer to changes in general cognitive measures, while measures of numerical cognition basically remained the same. Non-significant results remained equal in the first and second groups comparison analyses. Table 5 facilitates a comparative observation between the two performed analyses.

Table 5. Group differences found in both variance analyses

Tasks	1st comparison	2nd comparion
Raven (z-score)	TA>MLD	TA = MLD-Dis > MLD-nondis
Simple RT	-	-
Rey Complex Figure(copy)	TA>MLD	TA > MLD-nondis
Digit Span (forward)	-	-
Digit Span (backward)	TA>MLD	TA > MLD-nondis
Corsi Blocks (forward)	-	-
Corsi Blocks (backward)	TA>MLD	TA > MLD-nondis
Number writting (percentage)	TA>MLD	TA > MLD-Dis = MLD-nondis
Number reading	TA>MLD	TA > MLD-Dis = MLD-nondis
Simple Addition	TA>MLD	TA > MLD-Dis = MLD-nondis
Complex Addition	TA>MLD	TA > MLD-Dis = MLD-nondis
Simple Subtraction	TA>MLD	TA > MLD-Dis = MLD-nondis
Complex Subtraction	TA>MLD	TA > MLD-nondis
Simple Multiplication	TA>MLD	TA > MLD-Dis = MLD-nondis
Complex Multiplication	TA>MLD	TA > MLD-nondis
Oral Math Problem	TA>MLD	TA > MLD-Dis = MLD-nondis
Weber Fraction	TA>MLD	TA > MLD-nondis
Coefficient of variation (mean)	-	-

3.4. Discussion

The present study investigated the relevance of intelligence to the profile of children with Math learning difficulties, to ascertain the validity of the discrepancy criterion to diagnose. The main results were: 1) intelligence was not relevant to discriminate children with MLD and children with TA; 2) intelligence impacted the difference between groups only in measurements of global cognition, 3) but not in the numerical cognition. These topics are discussed as well as the validity of the discrepancy criterion to diagnose Math learning disabilities.

First, it is important to notice that in the definition of a cut-off point to identify children with difficulties, a liberal criterion (inferior quartile) was adopted, as recurrently done in the literature (Mazzocco, 2007). Also, all individuals presented normal intelligence (scores above PR 5). Although this study showed direct clinical implications, it is not possible to guarantee that the sample reached diagnosis criteria for learning disabilities, since our design was based on demographic measurements instead of clinical ones. On the other hand, genetic, cognitive, and behavioral differences are quantitative, and normally distributed in the population (Asbury & Plomin, 2013).

When children with MLD were compared to children with TA, groups presented differences in all domains assessed, except measurements of reaction time and short-term memory. In a second phase, as the group of children with difficulties was split according to the intelligence-school achievement discrepancy criterion, differences remained between children with TA and the MLD-nondis group. However, the MLD-dis group was no longer statistically different from the TA group in measurements of general intelligence and visuospatial skills, as well as specific Math measurements of subtraction, multiplication, and Weber fraction. The modification of the results can be attributed to compensatory mechanisms and association between measurements (Conway et al., 2002, Deary et al., 2007; Deary & Johnson, 2010; Asbury & Plomin, 2013).

Intelligence did not present a significant impact in discriminating groups with Math difficulties. This type of analysis is original, although there is a lot of evidence in the same direction associated with reading learning difficulties (Hoskyn & Swanson, 2000; Gresham & Vellutino, 2010; Stuebing et al., 2009). For each school difficulty, a specific cognitive domain is involved: in dyslexia, phonologic processing, and number sense for dyscalculia (Haase et al., 2014). In the present study, only the MLD-nondis group presented worse performance than the TA group in the number sense (Weber fraction), which could be associated with the global functioning of the discrepant group. Recent evidence points that adolescents with dyscalculia present more activation in brain regions related to a general domain when solving a magnitude comparison task (McCaskey et al., 2017). Since children with discrepant measurements presented better performance in general domain tasks, it is possible that a compensation effect occurred in their achievement. Regarding the absence of differences in subtraction and multiplication between TA and MLD-dis groups, they might also be associated with better general skills in the group with difficulties. The average age of children in all groups was around ten years old (4th grade) and, pedagogically, proficiency in these

Math skills was not expected, therefore identifying difficulties in the groups with poor Math achievement was not possible.

In the second comparison between groups, regardless of discrepancy between intelligence and Math achievement in the groups with difficulties, children with TA presented higher general cognitive skills than groups with difficulties. The diagnosis of learning disabilities is usually based on school achievement, and individuals that fit these categories are the ones that, besides specific deficits, do not present general cognitive skills good enough (in a normal distribution) to compensate and promote learning (Asbury & Plomin, 2013). Ferrer et al. (2010) discussed this topic showing that, in typical readers, there is a linkage between intelligence and reading abilities along their development. However, for children with dyslexia, even with intelligence in the normal range, there is a disconnection between reading and general cognitive skills. In addition, the group with reading difficulties presented a greater inclination of the development curve of general cognitive abilities in comparison to the curve of reading skills (Ferrer et al., 2010). In the research on Math learning difficulties, there is no consistent evidence, however, based on the results of the present study and the literature on dyslexia, the importance of cognitive and financial investments in this research topic is evidenced.

It is well known that intelligence is an important factor for diagnosing specific learning, disabilities, since difficulties raise through an unexpected achievement (APA,2013). However, are there benefits in diagnosing only individuals with significant differences between intelligence and school achievement? The movement against the discrepancy is not recent, and has risen lately (Sternberg & Grigorenko, 2002; Stanovich, 2005; Restori, Katz & Lee, 2009; Hale et al., 2010; 2016), having even been removed from the diagnostic manual in its last edition (APA, 2013). Our data indicates that intelligence is not crucial to identify the profile of children struggling with Math and, yet, there are no significant differences in the pattern of children with distinct learning difficulties. However, the validity of this criterion is related to questions that remain to be answered, and demands consideration of other diagnosis criteria (Taylor, Miciak, Fletcher & Francis, 2017).

The intelligence is the best-isolated predictor of life outcomes (Deary & Johnson, 2010; Hunt, 2011). However, there is no homogeneity in the measurements used in studies that investigate the influence of intelligence in learning disabilities. Several types of research, as the present one, choose quick and practical tasks that assess fluid intelligence that, from a

theoretical point of view, can be considered the synonym of g factor, an exact measure of global cognitive reasoning (Deary & Johnson, 2010). It is even more fragile when measurements of crystallized intelligence (i.g. WISC's vocabulary subtest) are used. Environmental influences for these tests are more significant (Deary & Johnson, 2010; Asbury & Plomin, 2013), and the performance of individuals might reflect both cognitive reasoning and sociocultural factors. In sum, the advancement of the discussion on the real validity of discrepancy criterion depends on more researchers integrating developmental, scholar, and clinical psychology, but also psychometry.

Children with learning disabilities present cognitive deficits and specific behaviors (Pennington, 2008; Haase et al., 2014) which directly impact tasks assessing intelligence. For example, children with dyslexic do not have reading habits, which negatively affects vocabulary improvement and, consequently, influences the assessment of intelligence (g factor). Besides, tasks as Raven's Progressive Matrices depend on visuospatial skills, which can be impaired in children with Math learning difficulties (Rourke, 1989; Venneri, Cornoldi & Garuti, 2003; Mammarella et al., 2017). To answer the question about the validity of the discrepancy criterion, should researches "discount" specific deficits in intelligence? Again, psychometry is needed in this discussion.

In this interface with psychometry, recent discussions on this topic turn even more complicated when the hypothesis that intelligence structure might be different between children with typical and atypical development, especially with learning disabilities, is inserted (Giofré & Cornoldi, 2015). This means that the organization of different components of intelligence, like verbal, nonverbal, processing speed, and working memory of children with typical development, can be different when compared to children with atypical development. Considering the psychometric assumption, intelligence is composed of factors or general and specific components, which are organized in hierarchical fashion, from the more general to the more specific (Andrés-Pueyo, 2006). Some evidence from recent studies using WISC-IV in the assessment of children with typical development and with learning disabilities suggest that the main difference is in working memory and processing speed factors (Cornoldi, Giofrè, Orsini, & Pezzuti, 2014; De Clercq-Quaegebeur et al., 2010). A recent investigation that compared 1383 children with specific learning disabilities to peers has revealed that measurements of discrepancies in WISC-IV were effective to identify differences between groups (Giofré, Toffalini, Altoè & Cornoldi, 2017). However, this hypothesis that there is a different intelligence structure for individuals with learning disorders is recent and has not

been deeply explored, especially considering the full cognitive profile of children with distinguishing learning disabilities (Math or reading deficits).

The purpose of the present study was not to question the validity of intelligence, but the discrepancy criterion instead. Intelligence is relevant to the neuropsychological achievement of children with Math learning difficulties, which was evidenced here in the group comparisons. The lack of difference in intelligence between children with TA and MLD attenuates effects in other skills, such that inferior intelligence scores negatively impacts school achievement in children. This kind of evidence is still scarce in the literature. To the best of our knowledge, this is the first work to ever show the role of intelligence in the profile of children with Math difficulties, selected by population criteria, and with a variety of cognitive tasks.

Finally, we defend that there is no diagnosis without a proper intelligence assessment, since this measure might be indicative of one's deficits' severity. Additionally, intelligence evidences the prognostic and the individual's response to intervention. The higher the general cognitive skills, the more resources that can be used to compensate the deficits (Deary & Johnson, 2010).

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4. COMT val158met and DAT1- 3'- UTR VNTR polymorphisms interfere with working memory performance of scholar children in Brazil

Aline Aparecida Silva Martins[1]; Annelise Júlio-Costa[2]; Pedro Motta Cassemiro[1]; Gabriela Chadid Salazar [1]; Vitor Geraldi Haase[2]; Maria Raquel Santos Carvalho[1]

[1]Laboratório de Genética Humana e Médica, Instituto de Ciências Biológicas, Universidade Federal de Minas Gerais, Brazil

[2]Programa de Pós-graduação em Neurociências, Universidade Federal de Minas Gerais, Minas Gerais, Brazil

[3]Department of Psychology, Graduate Program in Children's and Adolescents Health, Graduate Program in Psychology: Cognition and Behavior, Graduate Program in Neuroscience, Universidade Federal de Minas Gerais (UFMG), Instituto Nacional de Ciência e Tecnologia sobre Cognição, Comportamento e Ensino (INCT-ECCE)

ABSTRACT**:** Working memory (WM) is the capacity of temporary storage and manipulation of information. WM is crucial to the learning process, including arithmetics. Dopamine level is critical to modulate cognitive functions, such as WM, in the prefrontal cortex and striatum. Variations in catechol-O-methyltransferase (COMT) and dopamine transporter (DAT1 or SLC6A3) genes impair WM performance since they influence dopamine levels. Sex was also reported as an aspect that interacts with these polymorphisms. We aimed to evaluate the association of sex, COMT val158met and DAT1- 3'- UTR VNTR polymorphisms, and their interactions, on WM tasks performance and arithmetics achievement in a sample of nonclinical school-age children (aged 7-12 years). Subjects were evaluated regarding intelligence, arithmetics and working memory abilities. General Linear Models (GLM) were performed to dominance, codominance, and heterosis, for COMT val158met and DAT1-3'-UTR VNTR. Besides, sex was included as factor in all models. The results for COMT val158met polymorphism identified that boys met158met had the worst performance in verbal and visuospatial WM in the val-dominant model. In the met-dominant model, boys Met/- presented the worst performance in verbal WM. In the codominant model, the same pattern was observed, boys met158met scored lower verbal and visuospatial WM. Concerning DAT1-3'-UTR VNTR gene, we have found a significant association for verbal WM in the 9-dominant model: girls with at least a 9/- allele presented worse performance. In

the heterosis model, heterozygous girls also scored lower for verbal WM. No effect was found when arithmetics was the dependent variable. In COMT vs. DAT1 interaction model, no significant association was observed. These results suggested that sex interacts with COMT and DAT1 genes on WM tasks performance and, therefore, investigations on this field should consider different genetic models for each sex.

KEYWORDS: Working memory, catechol-O-methyltransferase (*COMT*) gene, dopamine transporter (*DAT1* or *SLC6A3*) gene, working memory tasks, genetic, cognition

4.1. Introduction

Working memory (WM) is the capacity of temporary storage and manipulation of information (Baddeley, 2012). WM has an important role in human cognition and cognitive performance, as understanding, learning, reasoning, decision making and also math learning (Baddeley & Hitch, 1974; Baddeley, 1992; 2000; Alloway et al., 2004; Raghubar et al., 2010). The most widespread cognitive model of working memory consists of three structures: a central executive that manages all mental activity and two slave systems - the phonological loop and the visuospatial sketch (Baddeley & Hitch, 1974; Baddeley, 2000). The first one retains and processes verbal-coded information (auditory or visual inputs), while the latter is specialized in visual and spatial coding for object identity and spatial relations, visuospatial sketchpad (Baddeley, 2000). Later, a fourth component was included in the model, the episodic buffer, which is responsible for integrating information from working memory with those retrieved from long-term memory (Baddeley, 2000). WM performance is a heritable trait varying of 15 to 72% (Ando et al., 2001; Chen et al., 2009; Lee et al., 2012; Vogler et al., 2014).

The brain area most related to working memory is the prefrontal cortex (Kane & Engle, 2002; Baddeley, 2012). Abilities attributed to a central executive component, such as manipulation, updated, inhibition, selection of information are mainly associated with bilateral activation of the dorsolateral prefrontal cortex (Gathercole, 1999; Baddeley, 2012; Eriksson et al., 2015). The phonological loop is a language related component and has a lateralized activation in the left hemisphere, including Broca's area and premotor cortex. Lastly, anterior occipital, posterior parietal and premotor cortex areas, all in the right hemisphere, are related to visuospatial sketchpad (Gathercole, 1999; Baddeley, 2012; Eriksson et al., 2015).

Regarding molecular aspects, dopamine plays a prominent role (Dickinson & Elvevåg, 2009). Dopamine level is critical to modulate cognitive functions, such as WM, in the prefrontal cortex and striatum (Tunbridge et al., 2006; Júlio-Costa et al., 2015). Genes that control the levels and signaling of dopamine have an influence on WM performance (Bolton et al., 2010; Söderqvist et al., 2012). Variations in catechol-O-methyltransferase (*COMT*) and dopamine transporter (*DAT1* or *SLC6A3*) genes that regulate the dopamine levels in prefrontal cortex and striatum impair WM performance (Bertolino et al., 2006; Karlsgodt et al., 2011; Baetu et al., 2015, Sambataro et al., 2015).

The *COMT* gene has a functional polymorphism encoded by the variation of a single nucleotide (G→A) at position 158 (COMT rs4680). This substitution promotes the transcription of different amino acids: methionine or valine (Standaert & Galanter, 2009). Chen et al. (2004) found that the rate of dopamine degradation by *COMT* depends on the genotype of the enzyme, whereas individuals with the polymorphic type val158val metabolize dopamine more rapidly, while methionine homozygous individuals have a degradation rate between 1/3 to 1/4 lower than the other homozygous genotype. Heterozygous individuals have an intermediate rate of degradation.

The fact that COMT has polymorphic types with different metabolic rates leads to the emergence of populational subgroups with varying levels of dopamine in the synaptic cleft. In the last 20 years, this variation of dopamine levels has been associated with different cognitive and emotional profiles (Mier et al., 2010, Júlio-Costa et al., 2015). In adults, generally, the methionine allele was related to better cognitive measures (in particular executive functions and working memory). However, data for younger samples are inconsistent. According to Júlio-Costa et al. (2015), in the age group of 6 to 18 years-old, only 14 studies investigated if there was any polymorphic types differences in working memory tasks performances, and five of them were performed in clinical populations (Attention Deficit Disorder and Hyperactivity - ADHD). The results of the integrative review are inconclusive. Although few studies found differences between the groups (six out of fourteen), essential variables were not controlled. The research indicates that the main problems are: wide age range of the samples, how the polymorphism was stratified, the different measures of working memory and statistical tests (Júlio-Costa et al., 2015).

The first study that investigated the association between working memory measures and *COMT* polymorphism in children found better performance of met158met individuals (Diamond et al., 2004). However, these results were replicated only by two other studies. Barnett and coworkers (2007) found that ten-year-old scholars carriers of two methionine alleles scored higher on a counting span task than val158met and val158val children. The effect was more pronounced in males. Besides, the same evidence was found in research using dot matrix as working memory measure (Dumontheil et al., 2011). In contrast, Wahlstrom et al. (2007) and Howarth et al. (2014) showed that better working memory performance was attributed to heterozygous individuals. However, both studies used samples of older adolescents, and a different pattern may occur due to physiological increase in dopamine levels at this age. It is well-established prefrontal cortex activation by

dopamine works in a function of “inverted U” throughout human development (Vijayraghavan et al., 2007). While met158met genotype usually stands at the apex of the curve, during adolescence, due to the raising of dopamine levels, val158met genotype goes to the top of the curve. Studies investigating the effect of age and sex regarding the association between *COMT* and working memory tasks performance are required. Barnett et al. (2007) was the only study which considered possible sex influence in the association between COMT rs4680 and working memory abilities.

COMT val158met polymorphism was implicated in the expression of ADHD symptoms, a condition in which deficits in working memory and learning disabilities are often observed. Nobile et al. (2010) demonstrated a moderation effect between this COMT genotype and socioeconomic levels. Children and adolescents valine homozygotic and belonging to a lower socioeconomic level had a higher risk of developing ADHD symptoms. Two other recent investigations recruited samples of children with ADHD to explore the relationship of COMT val158met polymorphism, WM, and other symptoms of this disorder. Jin et al. (2016) found that, in ADHD, met carriers children had better cognitive scores than the val homozygotes. Additionally, val homozygotes presented better performance in comparison to met carriers control children. Authors claimed this COMT polymorphism might impact WM abilities differently in children with and without ADHD (Jin et al., 2016). Furthermore, O’Donnell et al. (2017) observed, in a longitudinal study, that COMT rs4680 moderated the association between maternal prenatal anxiety and child ADHD symptoms and WM capacity. Valine homozygous showed a stronger effect compared to the other genotypes. Results were verified for two different cohorts (O’Donnell et al., 2017).

Beyond the WM and COMT rs4680 association, our research group found a relationship between COMT and another cognitive ability: the number sense (Júlio-Costa et al., 2013), which can be defined as the most fundamental numerical processing ability (Dehaene & Cohen, 1995). The study, performed with typical children aged 7 to 12 years, revealed that the group with at least one methionine allele presented a more accurate numerical sense in two computerized tasks: comparison and estimation of non-symbolic magnitudes. This result maintained the rationale that the methionine allele is associated with better cognitive measures (Júlio-Costa et al., 2013). It is interesting to note in the argumentation of this finding that children with developmental dyscalculia present a number sense deficit (Piazza et al., 2010, Mazzocco, Feigenson, Halberda, 2011). The same study (Júlio-Costa et al., 2013) still found differences between polymorphic groups in a transcoding task, which

measures the ability to transcribe quantities in different notations (2↔dois↔**). The main model of transcoding assumes that it is asemantic, which implies there is no access to the numerical sense, and it depends on the working memory, the cognitive function focused on here (Barrouillet et al., 2004; Camos 2008).

Tan et al. (2007) were the first to establish the association between the COMT val158met polymorphism, WM, and arithmetic problem solving, in an exploration using event-related magnetic resonance imaging. The results showed individuals valine carriers had higher levels of dorsolateral prefrontal cortex activation than individuals met158met. This level of activity correlated with the operations that require working memory to be executed in the arithmetic tasks, but not to operations of long-term memory rescue. The increased activity in the dorsolateral prefrontal cortex during resolution of arithmetic problems in individuals with elevated COMT activity and faster dopamine metabolism (val158) can be interpreted as compensatory (Tan et al., 2007).

Besides *COMT* polymorphism, other genetic variation has been associated with working memory measures. The *DAT1* gene or *SLC6A3* encodes the dopamine transporter protein (DAT) in the striatum, responsible for the reuptake of dopamine in the presynaptic cleft (Brehmer et al., 2009). This gene contains a 40 base pair variable number of tandem repeats, of 3 to 13 repeats, in the 3'-untranslated region (3'-UTR - VNTR) at the 15th exon, which affects the efficiency of the expressed protein. The alleles with 10 and 9 40bp repeats are the most frequent (Vanness et al., 2005; Mitchell et al., 2000; Vandenbergh et al. 1992).

The most studies involving DAT1 gene polymorphism in children samples were executed in individuals with ADHD, a childhood disorder characterized by reduced executive function, including working memory deficits. Homozygotes individuals for the 10 repeats allele have lower ligation of DAT to dopamine, impairing the functioning of cognitive aspects dependent on neurotransmission, as WM. This allele is related to ADHD symptoms and high reaction time in children with such diagnosis (Shang et al., 2014, Faraone et al., 2014, Soderqvist et al., 2012, Stollstorff et al., 2010, Kebir et al., 2009, Demirapl et al., 2007, Cornish et al., 2005). Besides that, subjects carriers of the 9 repeats allele have presented higher prefrontal neuronal activity during WM test than those with 10 repeats alleles in a sample of adults (Bertolino et al., 2006).

A recent study identified an interaction effect between age and DAT1 gene polymorphism in the WM performance of adolescents with ADHD aged between 14 and 18 (Thissen et al., 2015). In adults, the presence of 10\6 DAT1 haplotype is associated with increased ADHD symptoms (Tong et al., 2015). Other studies identified that children aged 7 to 12 years and heterozygotes for 9/10 repeats had better performance in WM tasks than children homozygous for 10 repeats (Stollstorff et al., 2010; Soderqvist et al., 2012).

This gene-cognition connection has also been reported in training working memory studies, after which heterozygous preschoolers showed improvement in their measures (Söderqvist et al., 2012). Nevertheless, no evidence was found in older children and adolescents (Söderqvist et al., 2014). Regarding adults samples, there is no consistent direction of DAT1 gene polymorphism influence on WM task. However, this association has already been reported (Colzato et al., 2013; Gordon et al., 2013).

DAT1 and COMT genes are implicated in cognition and WM (Bolton et al., 2010; Soderqvist et al., 2012). However, few studies have investigated the influence of val158met in COMT gene and 3'-UTR VNTR in DAT1 gene in WM performance simultaneously. A study performed with healthy adults showed that DAT1 or COMT genotypes alone or in combination did not predict scores on the n-back task (Blanchard et al., 2011). Authors also did not find an association between sex, WM, DAT1, and COMT. The interaction of these two polymorphisms with WM abilities and arithmetics achievement has not been investigated in healthy children yet.

Therefore, we aimed to evaluate the influence of the polymorphisms COMT val158met and DAT1- 3'- UTR VNTR, and their interactions, on WM tasks performance and arithmetics achievement in a sample of nonclinical school-age children (aged 7-12 years). It was also intended to test different genetic models (dominance, codominance, and heterosis) regarding sex for working memory and arithmetics performance. We hypothesized that variations on dopamine levels caused by polymorphic influences would impact WM and arithmetics tasks performances, however, considering sample age and scarce previous results, it was not possible to define which genetic variation group would perform better. Sex association is rarely explored, but it has been reported, especially for the COMT val158met polymorphism. Thus, we supposed there could be a different regulation for boys and girls.

4.2. Methods

4.2.1. Participants and procedures

The study was approved by the local Ethics Committee, and children's participation required parents' written authorization as well as oral consent by the subjects. The sample was composed of individuals aged 7-12 years enrolled in schools of Belo Horizonte, Brazil. Subjects were tested in two different phases. Firstly, children were evaluated in groups of eight regarding intelligence and arithmetics achievement. For the second phase, subjects with intelligence level above percentile 15 were invited to an individual neuropsychological evaluation. Children were tested concerning verbal working memory (Digit Span), and visuospatial working memory (Corsi Blocks). Finally, parents were summoned to supervise biological data (blood or saliva) collection of their children. All procedures occurred at the children's schools. The final sample was constituted by 351 children that were genotyped for COMT val158met polymorphism. Twenty-three children were not genotyped for DAT1-3'-UTR VNTR since there were not enough biological material. Thus, a total of the 328 children were genetically analyzed regarding DAT1- 3'- UTR VNTR.

4.2.2. Genetic analysis

DNA was extracted from peripheral blood or saliva using saline precipitation protocol (Miller et al., 1988). COMT rs4680 (val158met) polymorphism was genotyped by TaqMan SNP genotyping assay. It was performed in ABI 7900 and analyzed with TaqMan Genotyper Software (Thermo Fisher Scientific, USA). *DAT1* 3'-UTR VNTR genotyping was performed by PCR and electrophoresis in 8% acrylamide gel.

4.2.3. Instruments

Raven's Coloured Progressive Matrices: General intelligence was assessed with the Raven's Coloured Progressive Matrices - CPM (Angelini et al., 1999). The z-scores were calculated based on the manual's norms.

Brazilian School Achievement Test (TDE; Stein, 1994; Oliveira-Ferreira et al., 2012): The TDE is the most widely used standardized test of school achievement with norms for the Brazilian population. It comprises three subtests: arithmetics, single-word spelling, and single-word reading. In the first phase, only the arithmetics subtest was used, which can be

applied in groups. Norms are provided for school-aged children between the second and seventh grade in z-score. This subtest is composed of three simple verbally presented word problems (i.e., which is the largest, 28 or 42?) and 45 written arithmetic calculations of increasing complexity (i.e., very easy: 4 − 1; easy: 1230 + 150 + 1620; intermediate: 823 × 96; hard: 3/4 + 2/8). Reliability coefficients (Cronbach α) of TDE subtests are 0.87 or higher. Children are instructed to work on the problems to the best of their capacity but without time limits.

Digit Span: a traditional measure of verbal short-term memory that composes Wechsler Intelligence Scale for Children 3ª edition (Figueiredo, 2002). Phonological short-term memory was measured by the forward order, and verbal working memory by the backward order. Z-scores were calculated by age to run the analyses.

Corsi blocks (forward and backward): this task is a corresponding visuospatial measure of Digit Span. The instrument is a wood base with nine specifically positioned fixed blocks. The examiner points the blocks in defined sequences that become progressively longer each time the child is able to repeat the last trial correctly. The test starts with sequences of two blocks and can reach a maximum of nine blocks. Performance was assessed in forward and backward orders according to Kessels et al. (2000). Span is determined by the longest sequence correctly repeated before two successive failures. Z-score was calculated by age to run the analyses.

4.2.4. Statistical Analysis

The statistical analyses were performed in SPSS software, version 20.0. First, it was investigated possible differences regarding sex, age, and intelligence. The results on the WM and arithmetics tasks were evaluated for central tendency and dispersion (standard deviation) between different groups, separated according to genotypes. General Linear Models (GLM) were tested for dominance, codominance, and heterosis, for COMT val158met and DAT1-3'-UTR VNTR. Genetic variations and sex were inserted as factors in the model. WM and arithmetics measures were used individually as a dependent variable. COMT vs. DAT1 interaction models were used to contrast genotypes with putatively higher (Met/- and 10/-R) and lower (Val/- and 9/-R) dopamine concentration in the synaptic cleft. Hardy-Weinberg equilibrium test was run at GenePop on the web (Raymond & Rousset, 1995; Rousset, 2008).

4.3. Results

A total of the 351 children were genotyped for COMT val158met polymorphism. The genotype frequencies were: 1) homozygous children for the valine allele (val158val *COMT)*: n = 126 (35,9%); 2) heterozygous children (COMT val158met*)*: n = 173 (49,3%); 3) homozygous children for the methionine allele (met158met *COMT*): n = 52 (14,8%). Regarding the *DAT1* 3'-UTR VNTR genetic variation, a total of the 328 children were genotyped: 1) homozygous children for the 9 repeats allele (*DAT1* - 3'-UTR VNTR): n = 27 (7,7%); 2) heterozygous children (*DAT1* - 3'-UTR VNTR): n = 133 (37,9%); 3) homozygous children for the 10 repeats allele (*DAT1* - 3'-UTR VNTR): n = 168 (47,9%). Both COMT val158met and *DAT1*-3'-UTR-VNTR genotypes were in Hardy-Heinberg Equilibrium (p>0.05).

Regarding descriptive analyses, there was no differences in sex, age and intelligence between COMT val158met and *DAT1*-3'-UTR-VNTR polymorphism groups (p>0.05) (Table1). Additionally, group differences were not found for codominant models (three genotypes in each polymorphism) for either WM (Corsi Blocks and Digit Span) or arithmetic tasks (Table1).

Table 1 - Participants` demographic data by genotypes of COMT val158met and *DAT1*-3'-UTR-VNTR

		DAT1-3'-UTR-VNTR genotypes					
		9/9	**9/10**	**10/10**	**x²**	**p**	**Effect size**
		n (%)	**n (%)**	**n (%)**			
Sex	Male	12 (8.3%)	64 (44.4%)	68 (47.2%)	1.77	0.41	0.09
	Female	15 (8.2%)	69 (37.5%)	100 (54.3%)			
		Mean (sd)	**Mean (sd)**	**Mean (sd)**	**F**	**p**	**Effect size**
Age (years)		9.19 (1.27)	9.15 (1.09)	9.26 (1.19)	0.32	0.73	<0.01
Raven		0.52 (0.91)	0.76 (0.74)	0.56 (0.85)	2.63	0.08	0.02
Digit Span Forward		-0.13(1.07)	0.06(0.99)	0.01(0.85	0.52	0.6	<0.01
Digit Span Backward		0.14(0.90)	0.08(1.10)	-0.12(0.95)	1.73	0.18	0.01
Corsi Blocks Forward		-0.22(0.92)	-0.10(0.93)	-0.04(1.04)	0.39	0.68	<0.01
Corsi Blocks Backward		-0.09(1.16)	-0.04(0.98)	-0.04(0.99)	0.03	0.97	<0.01
TDE aritmetics subtest		0.12(0.92)	0.10(0.88)	-0.05(0.98)	1.05	0.35	<0.01
		val158vamet COMT genotypes					
		val158val	**val158met**	**met158met**	**x²**	**p**	**Effect size**
		n (%)	**n (%)**	**n (%)**			
Sex	Male	54(34.0%)	78(49.1%)	27(17.0%)	1.23	0.54	0.06
	Female	72(37.5%)	95(49.5%)	25(13.0%)			
		Mean (sd)	**Mean (sd)**	**Mean (sd)**	**F**	**p**	**Effect size**
Age (years)		9.22 (1.15)	9.15 (1.12)	9.21 (1.32)	0.16	0.86	<0.01
Raven (z-score)		0.59 (0.85)	0.62 (0.81)	0.67 (0.83)	0.19	0.83	<0.01
Digit Span Forward		-0.05(0.87)	0.06(0.97)	-0.02(1.01)	0.5	0.61	0.03
Digit Span Backward		0.07(1.18)	-0.05(0.92)	-0.10(0.83)	0.96	0.5	<0.01
Corsi Blocks Forward		-0.10(0.10)	-0.10(0.97)	-0.02(0.92)	0.16	0.86	<0.01
Corsi Blocks Backward		0.01(0.10)	-0.13(0.95)	0.07(1.05)	1.19	0.31	0.01
TDE aritmetics subtest		0.04(0.89)	-0.03(0.97)	0.04(1.04)	0.23	0.8	<0.01

4.3.1. Associations analyses

Possible group differences among genotypes regarding sex were investigated using variance analysis (GLM) individual models for each dependent variable (Digit Span Forward, Digit Span Backward, Corsi Blocks Forward, Corsi Blocks Backward and TDE arithmetic subtest). For COMT val158met polymorphism, analyses for genetic models of val-dominant, met-dominant and codominant were performed.

Concerning a val-dominant model for val58met *COMT* polymorphism, no main effect was found for polymorphism or sex (all p's >0.679). However, an interaction effect was observed and indicated that boys met158met had the worst performance in Digit Span Forward ([$F(1,348) = 4.14$, $MSE = 3.604$; $p=0.043$, $\eta 2 = 0.012$]), Digit Span Backward ([$F(1,348) = 5.43$, $MSE = 5.47$; $p=0.020$, $\eta 2 = 0.016$]) and Corsi Blocks Backward ([$F(1,348) = 11.20$, $MSE = 10.58$; $p=0.001$, $\eta 2 = 0.032$]). Significative analyses are graphically represented in figure 1.

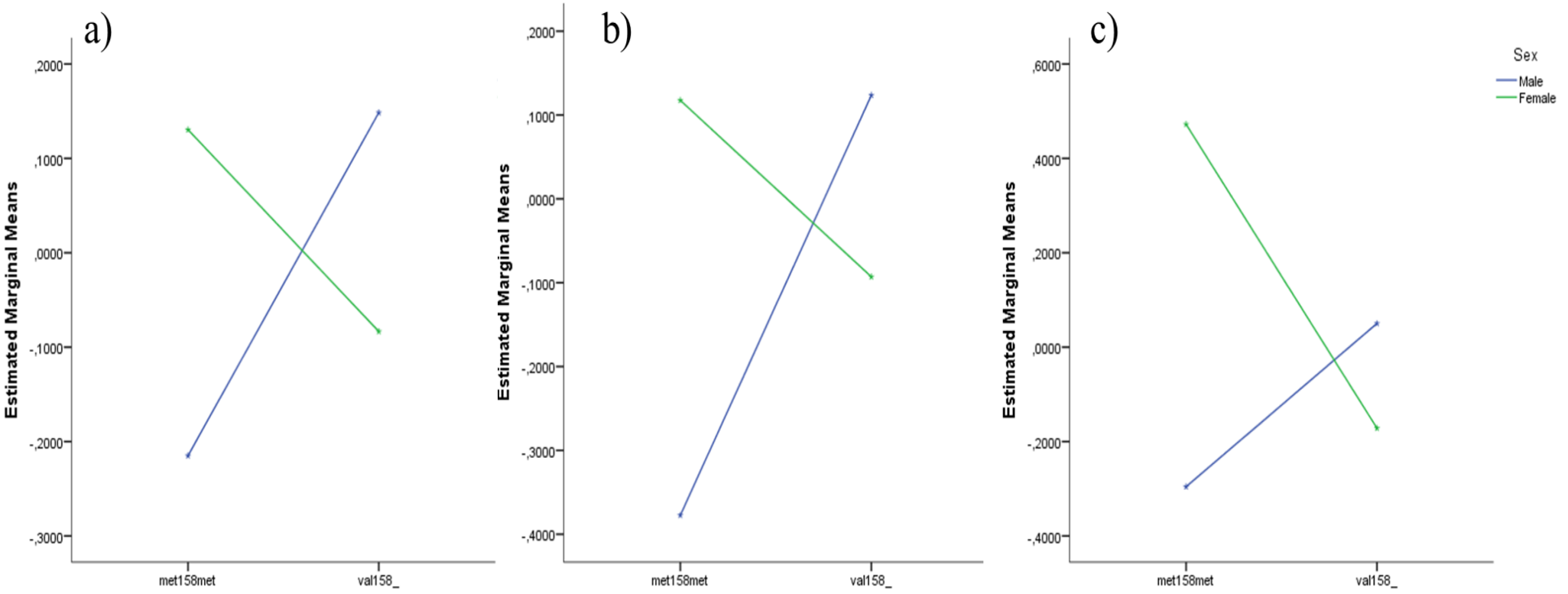

Figure 1: Distribution of estimated marginal means of a) Digit Span Forward (z-score); b) Digit Span Backward (z-score); c) Corsi Blocks Backward (z-score) for COMT genotypes in the val-dominant model.

When methionine was considered the dominant allele, only one effect was found. Sex interacts with COMT polymorphism in Digit Span Backward performance ([F(1,348) =4.69, MSE =4.77; p=0.031, η2 = 0.013]). Boys with at least one methionine allele exhibited the worst scores (Figure 2).

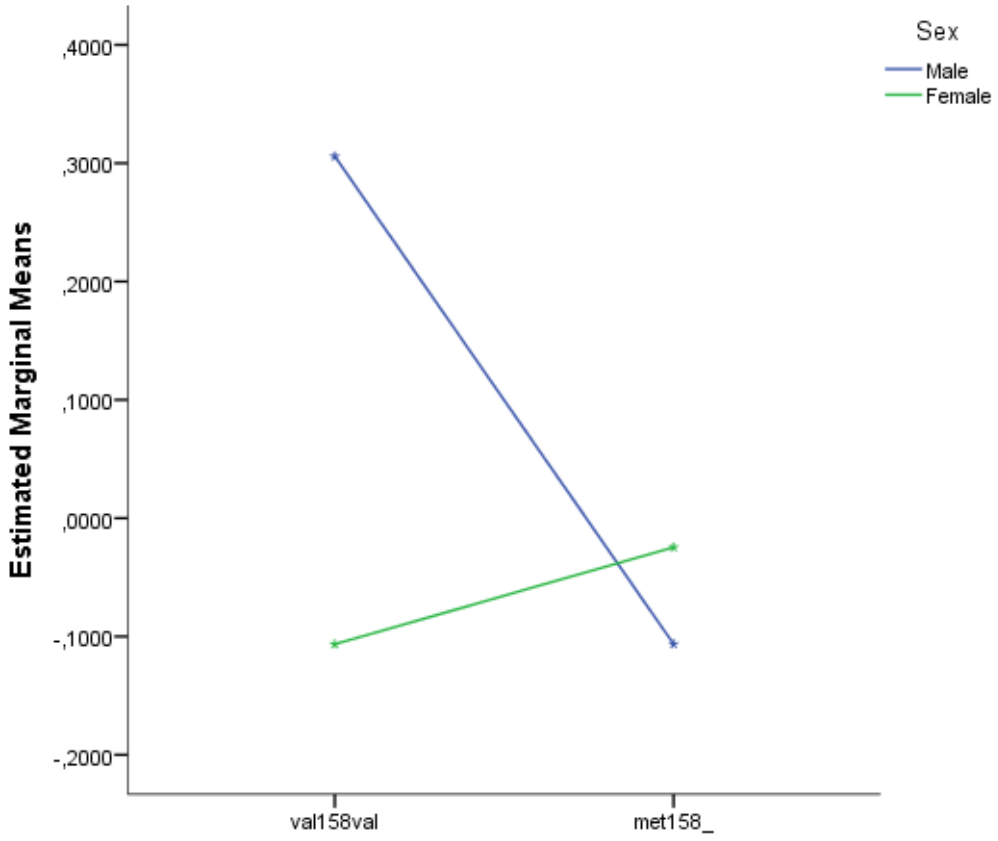

Figure 2: Distribution of estimated marginal means of Digit Span Backward (z-score) for COMT genotypes in the met-dominant model.

Finally, with the codominant model for COMT val158met polymorphism, the same pattern was observed: boys met158met COMT polymorphism scored lower in Digit Span Backward ([F(1,348) =4.39, MSE =4.43; p=0.013, η2 = 0.025]) and Corsi Blocks Backward ([F(1,348) =5.91, MSE =5.55; p=0.003, η2 = 0.034])). Heterozygous boys had intermediate measures while girls val158val e val158met performed similarly.

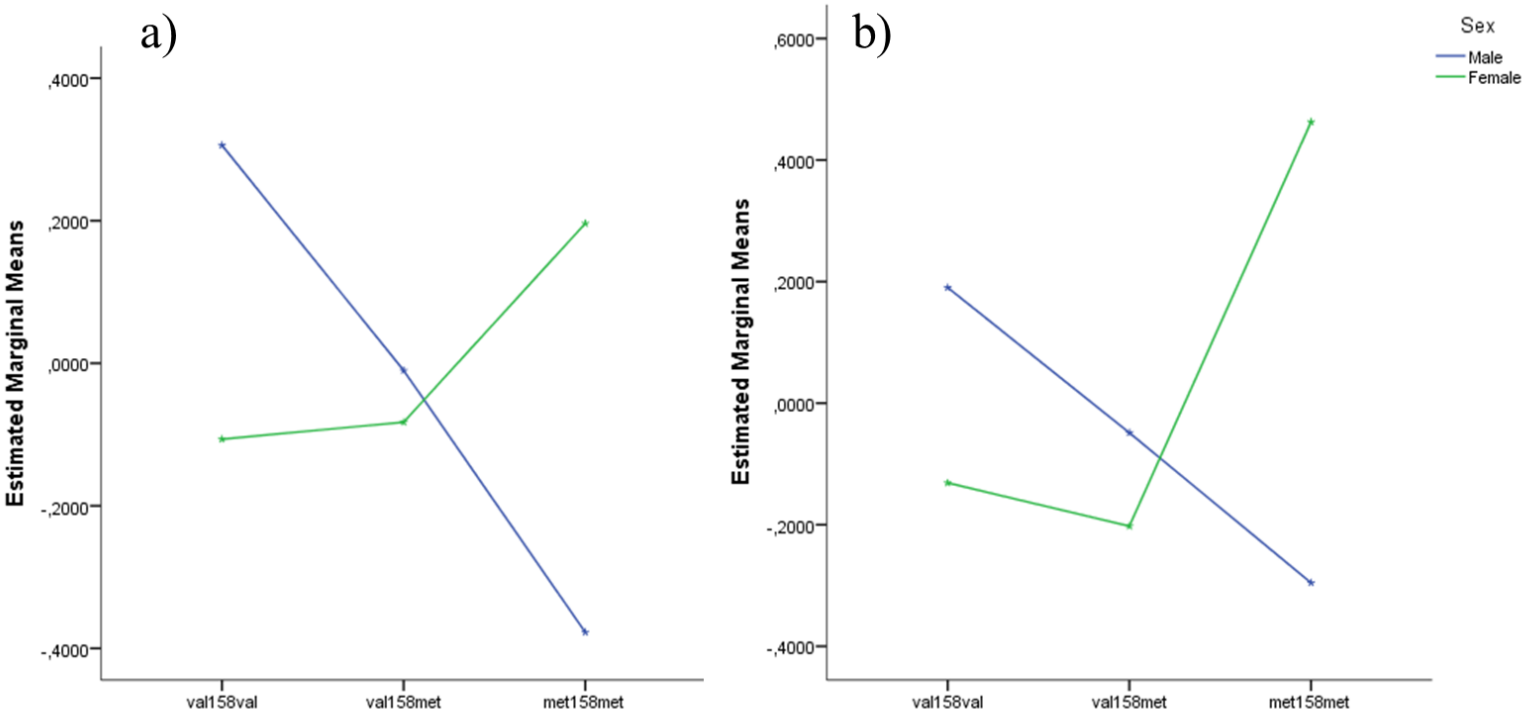

Figure 3: Distribution of estimated marginal means of a) Digit Span Backward (z-score); b) Corsi Blocks Backward (z-score) for COMT genotypes in the codominant model.

All genetic models were also implemented in arithmetics achievement (measured by TDE aritmetics subtest) analyses. There was no main effect for sex nor COMT val158met polymorphism (all p's >0.142). Interaction effects for all models were also not significant (all p's > 0.742).

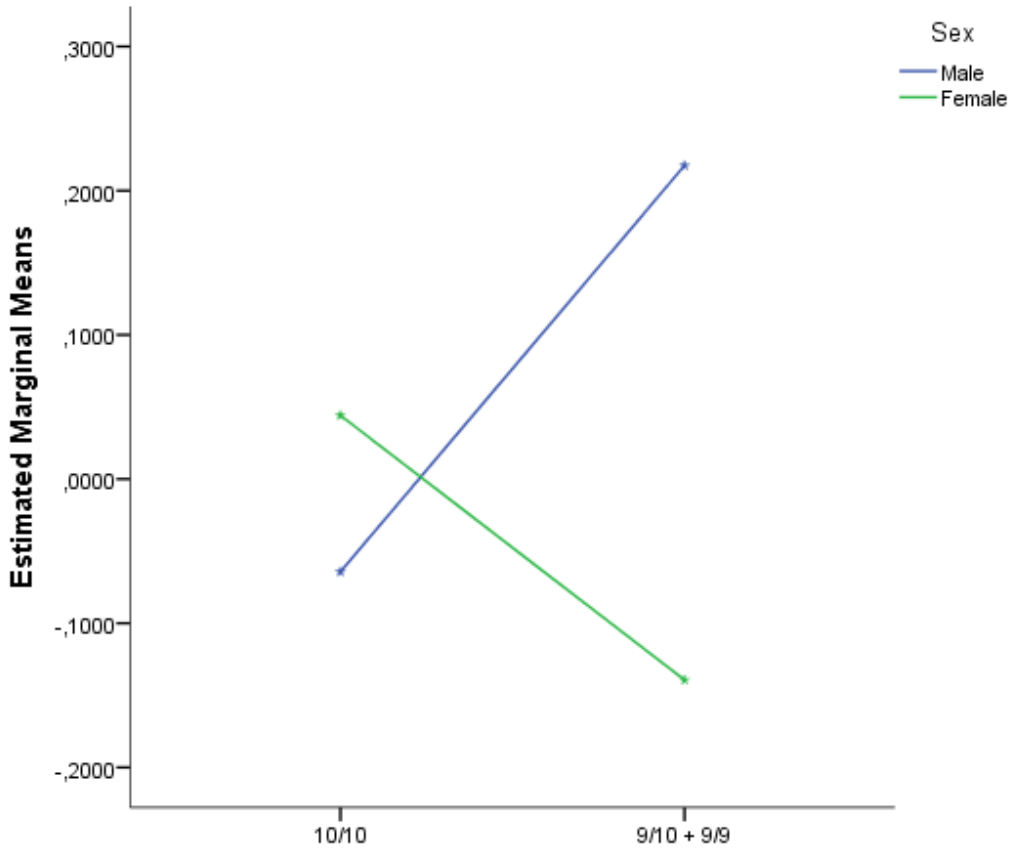

Figure 4: Distribution of estimated marginal means of Digit Span Forward (z-score) for *DAT1*-3'-UTR VNTR genetic variation groups in the 9-dominant model.

For *DAT1*-3'-UTR VNTR gene, 9-dominant, 10-dominant and heterosis genetic models were performed. In comparison to COMT val158met polymorphism, analyses for *DAT1*-3'-UTR VNTR exhibited fewer significant effects. A significant association between *DAT1*-3'-UTR VNTR genotypes and sex was found for Digit Span Forward ([$F(1,325) = 4.99$, $MSE = 4.27$; $p = 0.026$, $\eta 2 = 0.015$]) in the 9-dominant model: girls with at least a 9/- allele presented worse performance (Figure 4). In the heterosis model, an interaction effect for Digit Span Forward was observed ([$F(1,325) = 9.22$, $MSE = 7.78$; $p = 0.003$, $\eta 2 = 0.028$]) whereupon heterozygous girls scored lower (Figure 5). All significant results were described. Lastly, no effect (main or interaction) was observed for analyses regarding sex, *DAT1*-3'-UTR VNTR genes and arithmetics achievement (all p's > 0.272).

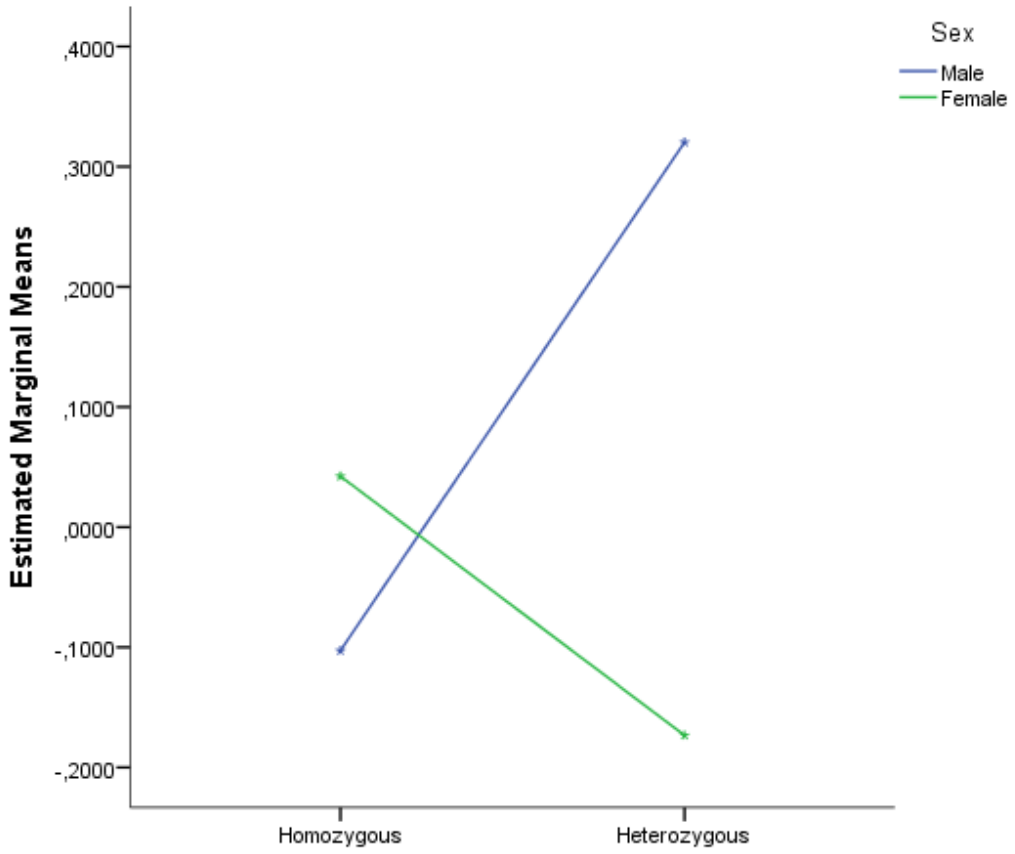

Figure 5: Distribution of estimated marginal means of Digit Span Forward (z-score) for DAT1 3'-UTR VNTR genetic variation groups in the heterosis model.

In *COMT* vs. *DAT1* interaction model with Met/- and 10/-R and Val/- and 9/-R, no significant association was identified for any dependent variable (all p's > 0.463).

4.4. Discussion

The COMT and DAT1 genes are involved in dopamine pathways in brain regions related to WM, as the prefrontal cortex and the striatum. Polymorphisms in these genes lead to dopamine levels deregulation, resulting in different WM profiles (Brehmer et al., 2009; Mier et al., 2010). The present study investigated the association between COMT val158met and 3'-UTR in DAT1 genes and scholar-age children's performance on WM tasks. These genes influences were also investigated on arithmetic achievement, which depends, at least partially, on WM. Main results may be summarized: a) COMT val158met polymorphism impacted sexes differently regarding WM scores, and boys met158met exhibited the lowest scores; b) there

was a consistent pattern through WM scores considering sex and COMT rs4680; c) concerning DAT1 3'-UTR VNTR polymorphism, the only effect found was for Digit Span Forward in 9-dominant model, and girls 9/- had the lowest scores. An effect in the same task was observed in the heterosis model, and the lowest performance was that of heterozygous girls. d) Regardless of the genes and the WM task, there was a similar and inverted performance pattern between boys and girls. Finally, f) genetic association was not found for arithmetics.

This study identified that boys with at least one methionine allele had a worse performance in WM tasks. Few studies investigated the association between the COMT val158met polymorphism and WM abilities in children, and fewer found its positive effects (Júlio-Costa et al., 2015). Children and adolescents over ten years old who are homozygous for methionine were better in visuospatial WM task - dot matrix - (Dumontheil et al., 2011), however, no effect was observed for younger children (aged between 6-9 years). On the other hand, Diamond et al. (2004) found that children met158met and aged between 6.8 and 14.6 years had the highest WM scores. Results differences may be attributed to the different tasks used to verify visuospatial WM. Besides, Diamond et al. (2004) did not separate children from adolescents.

Wahlstrom and coworkers (2007) evaluated WM abilities using Digit Span backward and Visuospatial Span backward performances in a nonclinical adolescents sample. Heterozygous individuals performed better in both tasks in comparison to met158met and val158val subjects. Howarth and coworkers (2014) also identified the highest verbal WM scores in the heterozygous group in a sample of children and adolescents with a brain tumor. Jin et al. (2015) found that COMT influence on WM is different in clinical and nonclinical children groups. In ADHD, methionine carriers had the best WM performance, however, in the control group the best scores were from the val158val individuals. None of the mentioned studies investigated the interaction amongst COMT polymorphism, sex, and WM. Only one study has explored such association in young samples. Barnett and colleagues (2007) identified that boys carriers of met158met genotype presented the best performance in Counting Span, a WM task, in comparison to the other genotypes.

In adults samples, previous studies found that val158val genotype presented the worst performance in cognitive activities in comparison to val158met and met158met genotypes. Val158met genotype showed intermediate performance (Egan et al., 2001; Heinzel et al., 2014). Studies investigating the interaction amongst sex, COMT genotype and WM tasks in

adults are conflicting. Gurvich & Rossel (2015) observed an association between sex and COMT val158met. Authors identified that women met158met exhibited a worse performance at time reaction in cognitive tasks than women val158val genotype. On the other hand, men val158val were worse at time reaction to complete the cognitive tasks than men with the genotype met158met (Gurvich & Rossel, 2015). This inverted pattern was also found here, in our younger sample. Goldberg and colleagues (2003), in a sample composed of patients with schizophrenia and controls, both male, also identified that individuals with val158val genotype had lower WM tasks performance than met158met genotype. Both investigations are similar to the present results, however, there is a samples' age difference.

Association between COMT and arithmetics was not found, such as in Tan et al. (2010) and Júlio-Costa et al. (2013). Nevertheless, both studies that demonstrated this interaction used more basic arithmetic tasks, as number writing and reading, number sense, number judging and single addition operations (Tan et al., 2007; Júlio-Costa et al., 2013). In contrast, TDE arithmetics subtest is a school achievement test and requires several numerical abilities. Thus, a good performance on TDE aritmetics subtest demands another gamma of cognitive skills. Besides, the more complex the task, the more difficult it is to investigate such matters using only SNP's of such polymorphism. The genetic variation explored here is minimal and may not be enough to impact a test that recruits a wider variety of cognitive abilities.

Regarding the DAT1 gene, the most frequent alleles identified were those with 9 and 10 repeats. In other studies, besides also being the most frequent, these alleles were related to neuropsychological disorders (Mitchell et al., 2000; Fuke et al., 2001). In addition, no differences in age or sex for genotype groups individually concerning WM and arithmetic measures were detected. These results are similar to those of other studies (Zilles et al., 2012; Brehmer et al., 2009; Wonody et al., 2009).

The one 9R allele (9/-) and homozygous (9/9) girls in the 9-dominant model (9/9 +9/10 X 10/10) or the heterozygous girls (9/10) in heterosis model (9/10 X 9/9 + 10/10) presented the worst performance in Digit Span Forward. These results contrast to other studies that identified individuals carriers of 10/10 genotype as the worst performers in the Digit Span task (Zilles et al., 2012; Brehmer et al., 2009; Sambataro et al., 2015). On the other hand, Wonodi and colleagues (2009) identified, in a sample of patients with schizophrenia, that individuals with 9/9 genotype had a worse performance than patients with 10/10 genotype in an eye movement task, which is similar to visuospatial WM tests. We found a significative interaction

amongst sex, DAT1 genotype and the Digit Span Forward in 9-dominant and heterosis model. This suggests that differences between sexes are influenced by the presence of the 9R allele.

There were differences in WM tasks performances of boys and girls considering polymorphisms involved in dopamine pathways. These differences can be contextualized by sex hormones that influence neuronal organizational changes constantly since the early stages of brain development (Duff & Hampson, 2001). Also, specific functions of the human prefrontal cortex are sexually differentiated, e.g., executive functions that include working memory abilities (Diamond, 2011; Duff & Hampson, 2001).

Evidence of the prefrontal cortex susceptibility undergoing organizational influence of sex hormones arises from the identification sex hormones receptors in the prefrontal cortex of nonhuman primates, such as rhesus monkeys (Handa et al., 1988). There is also evidence from human studies. Kaufman (2007) observed significative differences between sex in spatial and verbal WM tasks performance. Besides, the association between sex and spatial abilities was entirely mediated by spatial WM. Janowsky & Chavez (2000) found WM tasks scores improvement in older men who underwent testosterone supplementation, indicating that sex hormones may modulate WM in men, and that, consequently, such cognitive skill may be vulnerable to genetic variations. Furthermore, hormonal treatment in Turner syndrome girls is associated with improved cognitive abilities (Hong & Reiss, 2014). This is a genetic syndrome in which the second sexual chromosome is deleted, ie. individual has only an X chromosome in the classical form of this genetic condition. Ross et al. (2000) treated a group of Turner syndrome girls aged between 7 to 9 with an estrogen replacement therapy for approximately two years. One of the effects observed by the authors was that clinical group improved Digit Span (forward and backward) scores in comparison to placebo-treated age-matched girls.

In COMT vs. DAT1 interaction model with met158 and 10/-R and val158 and 9/-R, no significant association was identified. These results may suggest that there are no epistatic effects of these genes for performance in WM. However, this is the first study to investigate the interaction of the models that enable more (Met/- and 10/-R) or less (Val/- and 9/-R) dopamine to stay in the synaptic cleft and WM measures in a scholar children sample. In addition, we should consider that an investigation with more genetic factors may require a bigger sample than ours.

In summary, it was identified that genetic variables which act in dopamine bioavailability levels have an association with working memory abilities in scholar children, as previously reported

(Júlio-Costa et al., 2013; Dumontheil et al., 2011; Wahlstrom et al., 2007, Diamond et al., 2004). Nevertheless, new studies should augment investigation and consider sex influences, such as Barnett et al., 2007. Also, we found different genetic models that explain better this gene-cognition relationship for each sex. Therefore, new searches in this field must increase samples as well as stratify children and adolescents according to developmental stages, considering sex hormones levels.

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5. How is math scary for boys and girls? Math anxiety associated with sex by COMT val158met polymorphism

Annelise Júlio-Costa[1], Aline Aparecida Silva Martins[2], Guilherme Wood[3]
Maria Raquel Santos Carvalho[2] e Vitor Geraldi Haase[4]*

[1]Programa de Pós-graduação em Neurociências, Instituto de Ciências Biológicas, Universidade Federal de Minas Gerais, Brazil
[2]Laboratório de Genética Humana e Médica, Instituto de Ciências Biológicas, Universidade Federal de Minas Gerais, Brazil
[3] Departament of Neuropsychology, University of Graz, Austria
4. Department of Psychology, Graduate Program in Children's and Adolescents Health, Graduate Program in Psychology: Cognition and Behavior, Graduate Program in Neuroscience, Universidade Federal de Minas Gerais (UFMG), Instituto Nacional de Ciência e Tecnologia sobre Cognição, Comportamento e Ensino (INCT-ECCE)

ABSTRACT: Math anxiety (MA) is a specific phobia that appears in response to math tasks and situations which are perceived as a threat. MA elicits cognitive, affective, psychophysiological and behavioral reactions. Math anxiety impairs math performance and math difficulties increase MA. MA is more frequent and intense in persons of the female gender. This could be related to a greater susceptibility of the female, or to a lower susceptibility of the male, sex. Genetic factors may also play a role. Heritability of MA is substantial but, so far, no investigation has been conducted on the molecular-genetic basis of MA. The COMT (Catechol-O-Methyltransferase) val158met polymorphism could be part of the genetic underpinning of MA. The val158met polymorphism plays an essential role in dopaminergic pathways, especially in the prefrontal cortex. Thus, the aim was to investigate whether there were differences between the COMT val158met polymorphism groups in the math anxiety levels and arithmetics performance in 7-12 years children also considering sex influences. Girls scored higher than boys in math anxiety measured by Math Anxiety Questionnaire (MAQ). There was no average difference between polymorphic groups regarding the MAQ or math achievement. No main effect of the polymorphism was observed for sex. An interaction between sex and COMT polymorphism in the association with MA levels was observed. COMT val158val boys were significantly less anxious than the average of all children. COMT val158val girls were significantly more anxious than the average of all children. This interaction was specific to the MAQ scale assessing the affective aspects of MA.

The interaction between the COMT val158met polymorphism, MA and sex is due only to the valine homozygous genotype, as homozygous boys scored lower and homozygous girls higher in MA. The COMT val158val homozygosity could be related to an enhanced affective risk of MA in girls. The COMT val158val homozygosity is probably just a genetic marker of susceptibility that interact with other neurometabolic systems implicated in anxiety (such as the 5-HTTP gene) and cognitive processing (such as working memory). According to the diathesis-stress model of etiology, MA could emerge from a genetic susceptibility (COMT val158met) interacting with environmental experiences (stereotypic trait, i.e.).

KEYWORDS: COMT, Catechol-O-Methyltransferase, math anxiety, sex dimorphism, dyscalculia, social phobia

5.1. Introduction

Math anxiety (MA) definitions usually focus on math performance or on math self threats and beliefs (Chinn, 2009). Richardson and Suinn`s (1972) definition focus on performance: a "feeling of tension and anxiety that interferes with the manipulation of numbers and the solving of mathematical problems in a wide variety of ordinary life and academic situations" whereas Ashcraft and Faust`s (1994) definition focus on the self: "feeling of tension, helplessness, mental disorganization and dread produced when one is required to manipulate numbers or to solve mathematical problems".

Symptoms of MA resemble those of specific phobias (Faust, 1992). Predisposed individuals learn to react with anxiety to math-specific stimuli and situations. MA manifests itself at different levels: cognitive (negative attitudes, worrisome rumination, feelings of helplessness, low self-esteem and self-efficacy, etc.); affective (dysphoria); behavioral (avoidance, hurry-up to finish math tasks, etc.); and physiological (sweating, trembling, high pulse rate, etc.). Although MA is a mulltidimensional construct, it is usually measured through self-report scales focusing on two dimensions: cognitive (perceptions and beliefs) and affective (emotional reactions and feelings) (Haase, Guimarães and Wood, in press). Manifestations of MA are similar to those of other performance-related anxiety conditions such as reading, test, and social anxiety (Furmack, 2009). A connection with social phobia is suggested by the fact that MA levels increase from childhood to adolescence and college-age as well as associated feelings of shame and fear of losing face. The connection with other anxiety constructs is evidenced by low to moderate correlations (Hembree, 1990).

The clinical, educational and social relevance of MA is enormous in our increasingly knowledge-relying society. However, it is difficult to translate the impact of MA in more precise figures. Definitions and measures of MA rely on self-report measures applied to samples of students at different grades. There are no gold standard criteria identifying MA levels critically associated with untoward consequences. Prevalence rates are established on the basis of arbitrary cut-off levels, such as the 75th percentile. Thus, prevalence rates vary widely from 2-6% to 68% according to the sample and diagnostic criteria investigated (Dowker, Sarkar and Looi, 2016).

On the one hand, MA is important because of its association with math achievement. Correlations between MA and math achievement are usually negative and in the moderate

range (Hembree, 1990). The relationships between MA and math achievement are complex, bidirectional, and based on several mechanisms. Individuals with low math achievement, such as observed in developmental dyscalculia, are at risk of developing MA (Rubinsten and Tannock, 2010). MA interferes with math achievement in the short and the long run through both cognitive and behavioral mechanisms (Haase et al., in press). Interference with working memory processing is the main mechanism by which MA impairs math performance on the short run (Suárez-Pellicioni et al., 2016). On the long run, math achievement may be impaired by negative self-beliefs such as low math self-efficacy (Beilock et al., 2010). Behaviorally, avoidance of math-related activities reduces opportunities for learning both in the short and in the long run.

On the other hand, MA is considered especially important in the female sex (Haase et al., in press; Dowker et al., 2016) and in certain professional categories such as nurses and elementary school teachers (Beilock et al., 2010, Hembree, 1990, McMullan et al., 2012). Issues involving gender, math achievement and MA are also complex. It is known for many years, that MA levels are significantly higher in females than males (Hembree, 1990). Gender differences are observed from young school age on and tend to increase with time (Dowker et al., 2012). Female proneness and willingness to admit anxiety symptoms (Chapman et al., 2007, McLean et al., 2011), gender stereotype threat (Spencer, Steele and Quinn, 1999), and social transmission of MA by female teachers (Beilock et al., 2010) are some of the hypotheses raised to explain the higher rates of MA in females.

Much attention has been devoted to gender stereotype threat as im important socio-cognitive mechanism underlying MA. In situations where women are reminded of the stereotype that males are better at mathematics than females, their performance drops (Spencer et al., 1999). Neuroimaging indicates that gender stereotype threat in math situations activates ventral cerebral areas associated with negative emotional processing and inhibits dorsal areas relevant to controlled and math processing (Krendl et al., 2008). However, Stoet and Geary (2012) observed that studies only uncovered stereotype effects when prior math performance was statistically controlled. This may have attenuated the effects of previous math performance influences.

Thus, cognitive differences could underlie MA sex proneness. Average math performance in males and females is pretty similar. A tendency to girls increasingly obtaining better degrees than boys has been repeatedly observed (Dowker et al., 2012) A different picture emerges

when the extremes of the math achievement distribution are considered. Stoet and Geary (2013) observed sex differences favoring boys at the extremes of the performance distribution. These subtle but significant differences may be cancelled out when averaged. Additionally, higher MA levels in girls and undervaluation of girls' math abilities by parents seems to be independent of socioeconomic development and gender equity in a cross-national comparison (Stoet and Geary, 2016). In another study, lower MA levels in boys were mediated by better visuospatial processing abilities (Maloney et al., 2012). These subtle but potentially relevant cognitive differences could originate from fetal testosterone levels (Stoet and Geary, 2016). Supporting this hypothesis, a low negative correlation has been observed between 2D:4D digit-ratio, a marker of fetal testosterone levels, and related constructs such as computer anxiety (Brosnan et al., 2011, de Bruin et al., 2006).

A diathesis-stress model could thus be advanced to explain sex differences in MA. According to this hypothesis, higher MA levels in females could be the output of interactions between specific neurocognitive vulnerabilities and environmental stress sources such as gender stereotype threat. Testing of this hypothesis requires a deeper understanding of the neurobiological and especially the genetic bases of MA.

Neuroimaging research indicates that MA functionally inhibits dorsal hippocampus-derived regions associated with controlled and math-related processing such as the posterior parietal and dorsolateral prefrontal cortices (Young et al., 2012). At the same time, MA activates ventral areas related to fear processing, such as the amygdala (Young et al., 2012), anterior insula, related to body discomfort and pain, and cingulate gyrus, related to monitoring, social rejection and psychological suffering (Lyons and Beilock, 2012). Activations in the insula and cingulate cortices are more salient in the anticipation than during the execution of math activities (Lyons and Beilock, 2012). These results are analogous to those obtained in other forms of social anxiety. For example, hyperactivation of the cingulate cortex has been linked to feelings of rejection, embarrassment and shame (Bastin et al., 2016, Eisenberger, Liberman and Williams, 2003).

Two behavioral genetic studies investigated MA in twins (Malanchini et al., 2017, Wang et al., 2014). Heritability estimates around 40% were moderate. Genetic correlations were observed with other forms of anxiety such as general anxiety and spatial anxiety. Both shared and non-shared environmental influences were uncovered. Wang and coworkers` results suggest that MA emerges from the interaction between genetic influences on math performance and

general anxiety. General anxiety, by its turn, emerges from the interaction between its own genetic and nonshared environmental influences. Malanchini and coworkers (2017) obtained similar results, indicating a role for genetic and non-shared environmental factors, and for both shared and specific genetic influences on spatial and math anxiety. No genetic or environmental sex-specific pathways were investigated in these two studies.

To the best of our knowledge, no previous research has addressed the molecular-genetic underpinnings of MA. Other forms of anxiety have been associated with a host of genetic polymorphisms in several neurochemical systems (Stein et al., 2017). In this article, we focus on the dopaminergic system, as this system has been implicated in various forms of performance anxiety (Mathew and Ho, 2006). Genetic polymorphisms in the val158met locus of the COMT (Catechol-O-MetylTransferase) gene are a possible source of gender variability in math achievement and MA. The 158 position of the COMT gene may be occupied either by valine or methionine, defining a genetic polymorphism with functional consequences. Three genotypes are thus defined: val158val, val158met and met158met, with consequences for the enzyme's rate of catabolism. The presence of valine comparatively to methionine is associated with higher COMT metabolism and lower dopaminergic availability at the synaptic cleft (Chen et al., 2004). This COMT polymorphism has been shown to be important for several cognitive and emotional functions regulated by the prefrontal and parietal cortices, such as working memory (Júlio-Costa et al., 2015, Mier et al., 2010), numerical cognition (Júlio-Costa et al. 2013; Tan et al., 2007), impulsivity (Stein et al., 2006), anxiety (Gottschalk and Domschke, 2017; Mier et al., 2010), and psychiatric conditions such as schizophrenia (González-Castro et al., 2016), ADHD (Bonvicini, Faraone and Scassellati, 2016; Kebir and Joober, 2011), autism (Nikolac Perković et al., 2014), etc.

Early results suggested that the valine allele was associated with lower working memory performance and impulsivity (MIer et al., 2010, Stein et al., 2006). The methionine allele was, otherwise, implicated in higher working memory performance and anxiety. The connection between COMT val158met and arithmetic problems was explored in a study using event-related fMRI by Tan et al. (2007). Adult carriers of the valine allele had higher levels of dorsolateral prefrontal cortex activation than individuals with other genotypes. This activation correlated with arithmetic operations that require working memory, but not with the operations of long-term memory retrieval. The increased brain activation during resolution of arithmetic problems in individuals with valine allele may be interpreted as a compensatory mechanism (Tan et al., 2007). In addition, in a study performed with typically developing children aged 7 to

12 years, the group with at least one methionine allele displayed more accurated non-symbolic number magnitude comparisons as indexed by the internal Weber fraction (w) (Júlio-Costa et al., 2013). The authors also found differences between polymorphic groups in the same direction in a number transcoding task, which measures the working memory demanding ability to transcribe quantities in different notations (2↔dois↔**).

The COMT val158met polymorphism association with cognitive and emotional functions is subject to influences by culture, age and gender in adult samples (see reviews in Lee and Prescott, 2014, Barzman et al., 2015). The COMT val158met polymorphism has been variously implicated in anxiety manifestations in males and females (Hosak, 2007; Harrison and Tunbridge, 2008). Early reviews pointed out that both the valine and methionine alleles could be associated with anxiety-related phenotypes such as personality traits (e.g., neuroticism) and related disorders, i.e., generalized anxiety and panic (Harrison and Tunbridge, 2008; Domschke et al., 2007). Interactions with sex were also extremely variable and complex, with a tendency for genotypic-phenotypic associations being more salient in females.

Recent research also supports a nuanced picture of the association between COMT genotypes and anxiety manifestations. For example, Chen and coworkers (2011) found a COMT-by-sex interaction effect on affect-related personality traits in a large sample of the Chinese population. Homozygous males for valine showed significantly higher scores on negative emotions, and lower scores on positive emotions when compared with females. These results suggest that the associations between effects of the COMT val158met polymorphism and anxiety-related manifestations are complex and moderated by sex. The val158met polymorphism (rs4680) was observed to interact with sex and neuroticism but not with clinical symptoms of anxiety (Lehto et al., 2013). The interaction with neuroticism was investigated at three different ages (15, 18 and 25 years) in the same cohort. Valine homozygous females presented higher levels of neuroticism in the last assessment. In another study, females with at least one valine allele presented a tendency for higher levels of state and trait anxiety, lower RTsm when viewing faces expressing fear or anger (Domschke et al., 2012). Statistically significant higher activation rates were observed through fMRI in the ventral visual stream, amygdala, and lateral prefrontal cortex.

It has also been shown that estrogen has a down-regulatory effect on COMT activity; i.e., this female hormone reduces the rates of enzyme activity (Gogos et al., 1998; Xie et al., 1999;

Jiang et al., 2003). A meta-analysis suggested complex interactions between the COMT val158met polymorphism and menstrual phase and use of hormonal birth control (Lee and Prescott, 2014).

The complexity of the interactions between the COMT val158met polymorphism and sex is also reflected in studies with children and adolescents. In general, studies with children have shown that the COMT val158met polymorphism may act as a moderator between different kinds of anxiety manifestations in hetero-report measures and environmental stressors such as early emotional trauma and maternal anxiety. Some studies have implicated the met allele (Baumann et al., 2013; Olsson et al., 2007) and other studies have implicated the val allele (Sheikh et al., 2017; 2013). A dose effect for the met allele was observed in the Olsson and coworkers` (2007) study, which also interacted with the 5-HTTLPR gene. A larger effect was observed for the combined action of COMT met158 and 5-HTTLPR S alleles.

However, other studies report negative results, failing to find involvement of the val158met polymorphism with anxiety and the interaction with sex (Evans et al., 2009). The current state of knowledge does not allow generalizations regarding the importance of COMT val158met polymorphisms for anxiety, role of the alleles involved, interactions with other genes and hormones, and interactions with sex and age. This is illustrated in Table 1, which analyses the methods and results of the ten original articles from PubMed in January 2018 using the key words "COMT AND anxiety AND child*". Thirteen articles of the 23 retrieved were excluded because they did not investigate human subjects, did not have sample compose of children, did not have comparison groups, and focused on psychotic and OCD symptoms.

In the current study, we were interested in investigating if the COMT val158met gene polymorphism is associated with math achievement and MA, and if and how these associations interact with sex in children of school age. Towards this end, we genotyped a group of demographically-select school-age children of normal intelligence for the COMT val158met polymorphism and assessed the children`s performance in a standardized math achievement test and in a MA self-report questionnaire. To the best of our knowledge, this is the first study to investigate the molecular-genetic underpinnings of MA.

Table 1: Studies investigating the association between the COMT val158met polymorphism and anxiety in children

	Study	Country of origin	Participants' age in years (sample size)	Study design	Genotype groups	Clinical Sample	Anxiety Measures	Statistical test	Between groups' difference	Sex differences	Interaction with stress
1	Arbelle et al., 2003	Israel	7-8 (n=98)	cross-sectional	val/val, val/met, met/met	no	Schedule for Affective Disorders and Schizophrenia for School-Age Children, Martin Temperament Assessment Battery and Achenbach Behavior Checklist	univariate ANOVA	Not observed	Not investigated	Not investigated
2	Olsson et al., 2005	Australia	14 and 24 (n=962)	longitudinal with 2 measures (10 years)	val/val, val/met, met/met	no	Clinical Interview Schedule-Revised (CIS-R)	logistic regression and ANOVA	met158met higher symptoms for persistent episodic anxiety	Risk effect of the Met allele was among females only	Not investigated
3	Olsson et al., 2007	Australia	14 and 24 (n=962)	longitudinal with 2 measures (10 years)	val/val, val/met, met/met	no	Clinical Interview Schedule-Revised (CIS-R)	logistic model	Double recessive interaction: persisting generalized anxiety were more than twofold reduced in COMT (met/met) and 5HTTLPR (Short-Short) individuals compared with the remaining cohort	No sex interaction observed	Exploratory stratified analyses suggested that genetic protection may be more pronounced under conditions of high stress although strata differences did not reach statistical significance.
4	Evans et al., 2009	England	6-7 (n=8431)	cross-sectional	met/met, met/valA, met/valB, valA/valA, valA/valB, valB/valB	no	Strengths and Difficulties Questionnaire (SDQ) and life event questionnaire	logistic regression models	Not observed	No sex interaction observed	anxiety and depression in adults; no direct effect or interaction between stress and COMT genotype
5	Gadow et al., 2009	USA	4-14(n=67)	cross-sectional	met/_, val/val	yes (Autism Spectrum Disorder)	Child Symptom Inventory-4 (CSI-4)	ANOVAs	marginally significant for teacher ratings of social phobia (0.06) (met+ higher levels)	Not investigated	Not investigated

6	Middeldorp et al., 2010	Netherlands	7, 10, 12, 14 and 18 (n=1240 (included 288 MZM and 320 MZF twins and 382 unique male and 392 unique female))	longitudinal with 5 measures (11 years)	val/val, val/met, met/met	no	Child Behavior Check List (CBCL) at ages 7, 10 and 12 and Youth Self Report (YSR) at 14 and 18 years	Factorial association model and path analysis	No effect was found for anxiety or depression	Not investigated	Authors did not investigate
7	Shashi et al., 2010	USA	7-16 (n=40)	cross-sectional	val_, met_	yes (chromosome 22q11.2 deletion syndrome)	Child Behavior Checklist (CBCL) and Computerized Diagnostic Interview for Children (C-DISC)	non-parameter (Mann-Whitney)	Val allele was associated with a higher frequency of anxiety disorders	No sex interaction observed	Not investigated
8	Sheikh et al., 2013 (Study 1)	USA	~3.5(n=476)	cross-sectional	val/val, met_	no	Preschool Age Psychiatric Assessment (PAPA)	non-parameter (Mann-Whitney)	children homozygous for the V*al* allele had higher levels of depressive symptoms	Not investigated	Not investigated
9	Sheikh et al., 2013 (Study 2)	USA	~3.5(n=409)	cross-sectional	val/val; met_	no	Early Childhood Inventory-4 (ECI-4)	non-parameter (Mann-Whitney)	children homozygous for the V*al* allele had higher levels of depressive symptoms	Not investigated	Not investigated
10	Lehto et al., 2013	Estonian	15, 18 e 25 (n= 593)	longitudinal with 3 measures (10 years)	val/val, val/met, met/met	no	Mini-International Neuropsychiatric Interview (MINI 500)	Mixed linear models, ANOVA or ANCOVA	higher neuroticism scores in Val homozygotes	Val homozygosity effect only in females by age 25	Not investigated
11	Sheikh et al., 2017	USA	~3 (n=409)	cross-sectional	val/val; met_	no	Child Behavior Checklist	regression-based framework	under high levels of stress, Val allele carriers had significantly higher symptoms of anxiety compared to the met allele carriers.	girls had significantly higher depressive and anxious symptoms; therefore, child sex was used as a covariate	Stress, measured by cortisol, moderated the association between COMT val158met polymorphism and anxiety

5.2. Materials and methods

5.2.1. Participants

Participants were recruited among the students of 1st to 6th-grades, enrolled in public and private schools in Belo Horizonte, Brazil. The sample comprised 389 children with ages ranging from 7 to 12 years (mean age=115.66 [sd = 12.97] months, 55.32% female) and normal intelligence (PR > 10). Children participated only after informed consent was obtained in written form from parents, and orally from themselves.

Val158met alleles distribution in the sample is consistent with Hardy-Weinberg equilibrium ($\chi(2)= 0.03$, $p < 0.05$). Participants were assigned to one of three groups according to their genotypes: 1) homozygous children for the valine allele (COMT val158val): n = 141 (36.2%), 2) heterozygous children (COMT val158met): n =186 (47.8%) and 3) homozygous children for the methionine allele (COMT met158met): n = 62 (15.9%).

5.2.2. Instruments

Raven's Coloured Progressive Matrices: General intelligence was assessed with the Raven's Coloured Progressive Matrices - CPM (Angelini et al., 1999). The z-scores were calculated based on the manual's norms.

Arithmetics subtest of the Brazilian School Achievement Test (TDE): This test is composed of three simple orally presented word problems (e.g., which is the largest, 28 or 42?) and 45 written arithmetic calculations of increasing complexity (e.g., very easy: 4 − 1; easy: 1230 + 150 + 1620; intermediate: 823 × 96; hard: 3/4 + 2/8). Specific norms for each school grade were used to characterize children's performance (Stein, 1994; Oliveira-Ferreira, et al., 2012). For the present study, the *z*-scores were calculated by grade.

Math Anxiety Questionnaire (MAQ): The present study used a Brazilian Portuguese validated and standardized version (Haase et al., 2012, Wood et al., 2012). The MAQ is composed by four basic scales of 6 items each ("self-perceived performance" (MAQ A - self-perceived), "attitudes towards mathematics" (MAQ B - attitudes), "unhappiness related to problems in mathematics" (MAQ C - unhappiness) and "anxiety related to problems in mathematics" (MAQ D - anxiety) according to the authors of the original British version (Thomas and Dowker, 2000). The MAQ items have the format of one out of four types of questions: "How good are

you at…" (MAQ A - self-perceived); "How much do you like…" (MAQ B - attitudes); "How happy or unhappy are you if you have problems with…" (MAQ C - unhappiness) and "How worried are you if you have problems with…" (MAQ D - anxiety). The last scale measures math anxiety explicitly. Each scale contains one item referring to one of the following six categories: mathematics in general, easy calculations, difficult calculations, written calculations, mental calculations and math homework. Individual items are structured as a 5-point Likert scale (coded 0 to 4) and assembled visually to help children to organize their responses. The higher the score, the higher is the math anxiety level. Reliability coefficient (Cronbach's α) of MAQ scales ranges between 0.74 to 0.88 (Wood et al., 2012). A z-score was calculated for each MAQ scales.

5.2.3. Procedures

Data collection took place in the participants' schools. At first, the intelligence test (Raven's CPM) and the arithmetic subtest of Brazilian School Achievement Test (TDE aritmetics subtest) were applied in groups of eight children. Subsequently, parents were called to a meeting to collect the biological material collection (peripheral venous blood or saliva). Finally, children also answered the math anxiety questionnaire individually in a quiet room.

5.2.4. Genetic Analyses

DNA was extracted from peripheral blood or saliva using saline precipitation protocol (Miller et al., 1988). COMT rs4680 (val158met) polymorphism was genotyped by two methods: 1-TaqMan SNP genotyping assay. Genotyping was performed in ABI 7900 and analyzed with TaqMan Genotyper Software (Thermo Fisher Scientific, USA). 2- Tetra-primer amplification refractory mutation system-polymerase chain reaction (ARMS-PCR), as previously described by Ruiz-Sanz et al. (2007). In approximately 20% of the sample, genotyping was double-checked by PCR-RFLP with the restriction enzyme Hsp92II, confirming the results obtained through TaqMan SNP genotyping assay. These procedures are described in Júlio-Costa et al. (2013).

5.2.5. Statistical Analyses

Group differences in the distribution of sex, age, and intelligence, as well as interactions with the COMT polymorphism, were determined. We explored influence of intelligence using correlation analysis and the impact of sex using t-student test. Since intelligence may

confound the interpretation of possible interactions between sex, COMT polymorphism, school achievement and math anxiety, this variable (intelligence) was included as covariate in further comparisons. The impact of the COMT polymorphism on school achievement and math anxiety was investigated by between-subjects analysis of covariance (ANCOVA). Moreover, to examine the interaction between this genetic variation, mathematics anxiety, and sex, we performed a four factorial ANCOVA using sex and COMT polymorphism as between-subjects factors, MAQ scales as dependent variables and intelligence as covariate. We investigated the effect of homozygosity for valine on math anxiety regarding sex calculating two different general linear models in which 1) COMT val158val boys were compared to all other children for math anxiety and 2) the same comparison was run for COMT val158val girls.

Finally, we performed ANCOVAs in which MAQ scales were the dependent variable, intelligence was covariate and the different genetic models for COMT (codominant, methionine dominant, valine dominant and heterosis) were independent variable. This last analysis stage was run by sex separately in order to explore the best genetic model to this factor. Values of p smaller than 0.05 were considered significant.

5.3. Results

We aimed at investigating the impact and interaction of COMT genotypes and sex on math anxiety (measured by age-standardized MAQ scores) and arithmetics performance (measured by grade-standardized TDE aritmetics subtest scores) in 7-12 years-old children. First of all, we analyzed demographic variables to exclude any possible biases of results. Ascertainment of genotypic homogeneity between groups is essential considering our goals. Assuming a co-dominance model, the three groups of COMT genotypes did not differ regarding sex, age (in months), intelligence, or school grade, with all p's> 0.85 (Table 2).

Table 2: Participants` demographic data by genotype

		Total	val\val	val\met	met\met	x^2	p	Effect size
		n (%)	n (%)	n (%)	n (%)			
Sex	Male	174 (44.7)	62 (44.0)	83 (44.62)	29 (46.78)	0.138	0.93	<.001
	Female	215 (55.3)	79 (56.0)	103 (55.38)	33 (53.22)			
		Mean (sd)	**Mean (sd)**	**Mean (sd)**	**Mean (sd)**	**F**	**P**	**Effect size**
Age (month)		115.66 (12.98)	115.84 (12.55)	115.52 (13.01)	115.65 (13.99)	0.25	0.98	<0.01
Intelligence (Raven z-score)		0.72 (0.77)	0.73 (0.75)	0.70 (0.78)	0.75 (0.80)	0.12	0.89	<0.01
Grade		4.02 (0.95)	3.99 (0.87)	4.02 (0.97)	4.10 (1.06)	0.26	0.77	<0.01

Firstly, we explored the association between math achievement with demographic variables. Intelligence had a positive and significative correlation with TDE - arithmetics subtest ($r=0.416$; $p <0.001$). No sex differences was found ([$t (1,388) = -0.395$; $p = 0.693$; $d = -0.041$]). To investigate possible differences between the COMT genotypes in arithmetic performance, the scores were compared between groups using intelligence as a covariate since these variables were correlated. Differences regarding COMT val158met polymorphism groups for TDE - arithmetics subtest, and no effect was observed (Table 3).

The interplay of arithmetics achievement, sex, and COMT polymorphism was inspected by performing a factorial ANCOVA. Sex and COMT were included as factors, intelligence as the covariate and the TDE - arithmetics subtest was the dependent variable. Main effects of sex and COMT val158met polymorphism were not found ([$F(1,382) = 1.06$, $MSE = 0.990$; $p = 0.305$; $\eta 2 = 0.003$]; [$F(1,382) = 0.481$, $MSE = 0.451$; $p = 0.619$; $\eta 2 = 0.003$], respectively), as well as no interaction between these two factors ([$F(2,382) = 0.115$, $MSE = 0.107$; $p = 0.892$; $\eta 2 = 0.001$]). However, there is a significant effect for Raven`s CPM ([$F(1,382) = 80.15$, $MSE = 75.124$; $p < 0.001$, $\eta 2 = 0.173$]), meaning that intelligence influences arithmetics performance and justify the use of an ANCOVA model.

Table 3: Math anxiety and math performance across genotypic groups

Tasks	val158val (n=141)	val158met (n=186)	met158met (n=62)	ANCOVA (Covariante: RAVEN)		
	Mean (sd)	Mean (sd)	Mean (sd)	F	p	η^2
TDE - arithmetics subtest (z-score)	0.27(1.03)	0.17(1.08)	0.30(1.07)	0.437	0.646	0.002
MAQ A - self-perceived	-0.04(1.02)	0.06(0.96)	-0.07(0.87)	0.576	0.563	0.003
MAQ B - attitudes	-0.01(0.97)	0.03(0.97)	-0.06(0.94)	0.178	0.837	0.001
MAQ C - unhappiness	0.02(1.00)	-0.05(0.95)	0.09(0.97)	0.548	0.579	0.003
MAQ D - anxiety	-0.01(1.03)	-0.02(0.90)	0.07(1.04)	0.208	0.813	0.001

Same analyses were performed for all MAQ scales. Intelligence correlated negatively and significantly only with MAQ - Scale A (r= -0.107; p = 0.035), but not with other scales (MAQ - Scale B → r= -0.013; p = 0.800; MAQ - Scale C → r= -0.057; p = 0.262; MAQ - Scale D → r=-0.072; p = 0.156). A t-student test was run to investigate difference between sex regarding math anxiety. No group distinctions among boys and girls were identified to MAQ - Scale A ([t (1,388) = -1.523; p = 0.129; d = -0.616]), MAQ - Scale B ([t (1,388) = 0.199; p = 0.843; d = 0.010]) and MAQ - Scale C ([t (1,388) = -0.313; p = 0.754; d = 0.003]). However, girls were statistically more anxious considered measurement MAQ - Scale D ([t (1,388) = -2.109; p = 0.036; d = -0.023]).

Intelligence was also included as a covariate when COMT genotypes differences was explored. No differences were found in the comparison between genotypic groups for any of the MAQ scales (Table 3). Next, we investigated the interaction effect between sex, COMT polymorphism and math anxiety, calculating again factorial ANCOVA models for each MAQ scale. Both main effects of sex and genotypes and a sex by genotype interaction were observed for MAQ - Scale D, which specifically measures affective/feeling aspects of math anxiety. Except for MAQ - Scale D (anxiety related to problems in mathematics), results for all other scales were nonsignificant (all p's > 0.198). In general, girls showed higher anxiety levels in MAQ - Scale D than boys (all girls: mean= 0.093[sd = 0.998], all boys: mean= -0.115[sd = 0.928] and the results revealed a main effect of sex (Table 3; [F(1,382)=4.901; p = 0.027; η^2 = 0.013]). Additionally, there was an interaction effect for MAQ - Scale D between sex and the COMT polymorphism ([F(2, 382)= 3.732; p=0.018; η^2 = 0.021]) (Table 4 and Figure 1). Inspection of Figure 1 suggests that the sex interaction is limited to homozygotic children for valine. COMT val158val boys had significantly lower levels in MAQ - Scale D than corresponding valine homozygous girls. Thus, the sex interaction in MAQ - Scale D seems specific to the COMT val158val children.

Table 4: Correlates of math anxiety (MAQ - Scale D): main effects of sex and sex by genotype interaction

	Sum of Squares	df	Mean Square	F	p	η^2
Intercept	0.379	1	0.379	0.410	0.523	0.001
Raven (z-score)	0.804	1	0.804	0.868	0.352	0.002
COMT polymorphism	0.413	2	0.206	0.223	0.800	0.001
Sex	4.535	1	4.535	4.901	0.027	0.013
Interaction COMT polymorphism x Sex	7.464	2	3.732	4.033	0.018	0.021
Error	353.501	382	0.925			
Total	366.392	389				
Corrected Total	366.392	388				

In order to investigate if the sex by MAQ - Scale D interaction was restricted to the COMT val158val children, we performed an additional comparison between COMT val158val boys versus all other children and between COMT val158val girls and all other children. COMT val158val boys were the statistically the least anxious group ([$F(1,386)= 7.08$; $p=0.008$; $\eta^2 = 0.018$]) and COMT val158val girls were the most anxious group ([$F(1, 386)= 5.08$; $p=0.025$; $\eta^2 = 0.013$]).

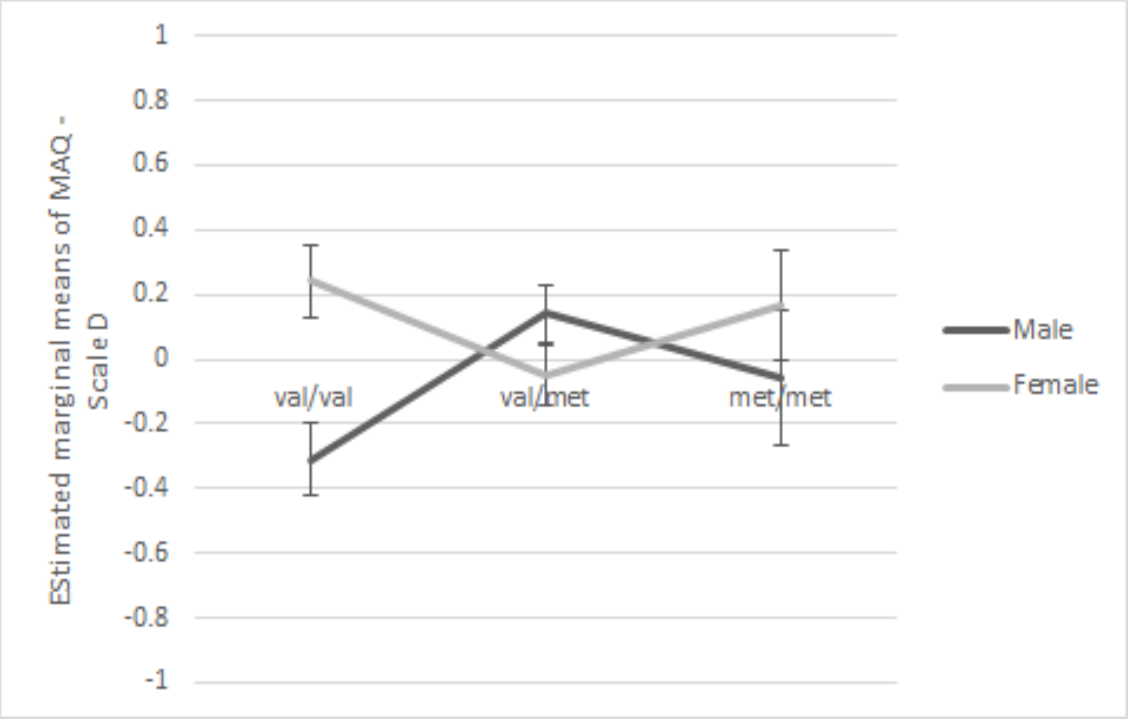

Figure 1: Relationships between sex, COMT val158met polymorphism, and math anxiety (MAQ - Scale D). The bars indicate the standard error of the group means.

We did a post-hoc analysis to inspect differences in genetic models for each sex considering specific measures of math anxiety (MAQ - Scale D). We performed models of codominance, valine dominance, methionine dominance, and heterosis. Different interaction models were significant for each sex. Concerning the group of girls, it was observed a significant effect only in the model in which homozygous girls (val158val+met158met) were compared to heterozygous girls ([$F(1,212) = 4.02$, $MSE = 3.97$; $p = 0.046$; $\eta 2 = 0.019$]). Lastly, a methionine dominant (val158val X met158_) was the best fitting model for boys ([$F(1,171) = 4.05$, $MSE = 3.41$; $p = 0.046$; $\eta 2 = 0.023$]).

5.4. Discussion

COMT polymorphisms have been associated with several different cognitive abilities such as reading (Landi et al., 2013), numerical processing (Júlio-Costa et al., 2013; Tan et al, 2007), as well as emotional manifestations such as general anxiety (Mier et al., 2010; Harrison and Tunbridge, 2008) and social phobia (Mathew and Ho, 2006). The present study investigated the association of the COMT val158met polymorphism with math-related emotions and performance. Our results can be summarized in the following terms: a) there was no average difference among polymorphic groups regarding the math anxiety levels and math achievement, b) however, there was a sex effect for math anxiety in which girls were more anxious. Additionally, c) there was an interaction between sex and COMT polymorphism in the regulation of math anxiety levels after that COMT val158val boys were significantly less anxious than the average of all children and d) COMT val158val girls were significantly more anxious than the average of all children. e) We have also found a different genetic model that best fit each sex regarding math anxiety: heterosis for girls and methionine dominant for boys. These results will be discussed in detail below.

The present study was the first to investigate the association between math anxiety and COMT polymorphisms in children younger than 12 years old. Only a few other studies have examined the association between the COMT polymorphism and anxiety traits in this age group. An investigation of typically developing 6-7 years old children found no evidence for an association between the COMT polymorphism and generalized anxiety (Evans et al., 2009). However, the negative results by Evans et al. might be due to the use of indirect measurement of anxiety (e.g., a questionnaire answered by the parents). On the other hand, it was found an association between COMT polymorphism and anxiety symptoms in a sample of 3-years-old (Sheikh et al., 2013). Authors found that COMT val158val children had more

depression and anxiety symptoms. A study investigating autistic children aged between 4 and 14 years suggested that the COMT polymorphism could be a biological marker of social phobia (Gadow et al., 2009). Our results indicate an association between COMT polymorphisms and math anxiety in typically developing 7-12 years old children.

We found a main effect of sex on math anxiety: girls are more anxious than boys. This difference has been identified along with all development including range investigated here (Dowker et al., 2012). There was different hypothesis for this: greater female propensity to report and admit feelings (Ashcraft et al., 2007; McLean et al., 2011,), social models as such teachers (Beilock et al., 2010) and social stereotypes (Spencer et al., 1999; Dowker et al., 2016). Previous studies have pointed out behavioral and neuroimaging evidence supporting psychosocial influence on the manifestation of math anxiety symptoms (Krendl et al., 2008; Beilock et al., 2010). Krend et al. (2008) observed increased activation of anterior cingulate areas (related to emotional regulation) only in those women in whom the gender stereotype was recalled to solve a mathematical task ("women are worse than men in math"). While in the control group women have activated only brain areas related to numerical performance when solving the same problems. Moreover, math anxiety of middle-school teachers had a negative impact on the performance of their female students, but not in the male ones (Beilock et al., 2010). Albeit sex differences for math anxiety are consistent (Dowker et al., 2016), there is no evidence of math performance (Lindberg et al., 2010). Although the main effect of gender observed in the present study may be attributed at least in part to the psychosocial causes enumerated above, the significant interaction between sex and COMT polymorphism we have found may certainly not.

We found that COMT val158val boys are significantly less anxious than the average of all children while COMT val158val girls were significantly more anxious than the average of all children. These results suggest that the association between math anxiety and the COMT polymorphism is limited to valine homozygous COMT polymorphisms and is established already in early age since the oldest participants of our study are only 12 years-old. In adults, an interaction between sex and COMT polymorphisms has been reported and indicates influence of this polymorphism on females (Hosak, 2007; Harrison and Tunbridge, 2008) and on male (Konishi et al., 2014; Lee and Prescott, 2014). The main evidence supporting this hypothesis of sex differences is the regulatory role of estrogen. This hormone has an effect of down-regulation of COMT which causes lower expression of the enzyme, therefore a negative feedback effect and a decrease dopamine release (Gogos et al., 1998; Xie et al., 1999; Jiang

et al., 2003; McDermott et al., 2015). Dopamine levels in female cortex are about 30% higher than in males, and the mechanism has been considering COMT activity (Chen et al., 2004). Levels of estrogen have been related to numerical cognition in adult samples (Pletzer et al., 2011). Since the main hypothesis for physiological anxiety disorder is related to the decrease of monoamines (among them dopamine), and estrogen appears in more significant quantities in women, it would be expected a greater vulnerability of this gender concerning men for anxiety (Harrison and Tunbridge, 2008). We had a young sample, but it is well-established that there is a significant difference between estradiol level of boys and girls (for review Roy et al., 2009). Accordingly, it is possible that estradiol explains the gender susceptibility in the relationship between math anxiety and visuospatial abilities (Maloney et al., 2012). Additionally, a recent study found sex differences regarding spatial anxiety and a significant correlation between it and math anxiety (Malanchini et al., 2017). Finally, sex differences found in implicit measures of math anxiety (Rubinstein et al., 2012) may be explained by this biological evidence in interaction with the environmental aspects.

Differences in math anxiety levels were accentuated by valine homozygosity. There is no previous study in a sample of primary school children. However, a meta-analysis with non-clinical samples of adults showed sex-specific and ethnic-specific homozygous effect: val158val individuals had the highest levels of neuroticism in white males and the highest harm avoidance in Asian men (Lee and Prescott, 2014). The authors observed no effect in women. On the other hand, women that carrier COMT val158val gene were better to identify sad expressions (Weiss et al., 2007). There are several evidences supporting attentional biases to negative emotions associated with anxiety symptoms in adults (Shackman et al., 2016) and children (Dudeney et al., 2015).

COMT polymorphism influence on emotional symptoms was tested in a large sample of more than eight thousand 6-7 years children (Evans et al., 2009). No effect was found for COMT polymorphism nor sex. However, Sheikh et al. (2013) showed that COMT val158val polymorphism was associated with internalized symptoms (depression and anxiety) in early childhood. Single nucleotide polymorphism, such as COMT, has become a focus of investigation regarding the influence of genetic variation on cognition and emotion. Although data have been found, they are inconclusive, and the direction of the association has not been clear. New studies are required, especially using aspects intermediate between genetics (polymorphisms) and behavioral (symptoms).

Regarding arithmetics achievement, the fact that no differences between COMT groups were found it is not surprising. Júlio-Costa et al. (2013) observed that children with at least one methionine allele were significantly better than those homozygous for valine in numerical tasks that assessed number sense and number transcoding. These skills have a relationship with performance in mathematics (Halberda et al., 2008; Costa et al., 2011, Pinheiro-Chagas et al., 2014). However, there is no direct link. Mathematics performance is a complex behavior that depends on specific factors (e.g., number sense) (Halberda et al., 2008), but also general cognitive domains (e.g., working memory) (Raghubar et al., 2010; Lukowski et al., 2015). Since groups were matched for gender, intelligence and grade a group difference determined by exchanging only a single nucleic acid, such as COMT polymorphism, seems to be not enough. Moreover, the more complex a behavior is, the more significant is the sample size required to demonstrate a SNPs effect, i.e. since the COMT genotypes influence on basic aspects of numerical cognition (Júlio-Costa et al., 2013) the investigation of this genetic variation impact in a more complex behavior (math performance) would require a sample size larger (Júlio-Costa et al., 2014).

Interestingly, from the four scales present in MAQ, only that one specifically related to math anxiety interacted with the COMT polymorphism and sex, although there are correlations between the different scales (Wood et al., 2012). As pointed out by Krinzinger et al. (2007) the first two scales ("MAQ A - self-perception performance", "MAQ B- attitudes in mathematics") are related to cognitive aspects, while the last two ("MAQ C- unhappiness related to problems in mathematics," and "MAQ D - anxiety-related problems in mathematics") to emotional/affective aspects. The study by Haase et al. (2012) that also used MAQ found differences between groups only in the scale of self-perception performance. However, a different criterion, based on difficulties in learning mathematics, was employed to split samples. Accordingly, children with poorer performance in math also perceived themselves as poor students in that discipline (Haase et al., 2012). Some other studies also show an association between performance and math anxiety (for review Dowker et al., 2016; Haase et al., in press), but those results should be interpreted cautiously since the combination of cognitive and affective factors has not been employed to characterize math anxiety in all of them. Accordingly, Krinzinger et al. (2009) observed that low performance is not a predictor of emotional (math anxiety), but of cognitive (perception of performance and attitudes) aspects. Those evidence are in line with majority studies (Haase et al., in press).

In summary, homozygosity of COMT val158val polymorphism has an impact on math anxiety levels in children, and this effect is determined by sex. Girls are more susceptible to the environment (Dowker et al., 2016; Haase et al., in press). Our data suggest that COMT polymorphism might be taken into consideration as biomarker candidate for math anxiety in girls. Boys homozygous for valine degrade dopamine at a higher speed, this lower rate of neurotransmitter in brain regions is associated with emotional control that is related to lower anxiety levels. Thus, genetics seems to be more decisive for boys since they are more resilient to environmental factors and being COMT val158val for COMT genes is a protection factor.

Our results suggest that besides the implications on cognitive aspects of numerical processing (Julio-Costa et al., 2013), COMT val158met polymorphism might be related to emotional aspects: math anxiety. Statistical differences were found between the polymorphic groups revealing worst emotion regulation in female children homozygous for valine allele. This study is the first to investigate the genetic basis of math anxiety. Further studies must aim to clarify this influence by increasing the sample size and including other neuropsychological measures (e.g., working memory) and polymorphisms (e.g., 5-HTTLPR) associated with math anxiety.

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6. Considerações finais

A presente tese teve o objetivo investigar aspectos genético-molecular e cognitivo relacionadas a aprendizagem da matemática e suas dificuldades. Apesar de apresentar estudos com evidências em diferentes níveis de análise, entende-se a matemática como um fenômeno único. A aprendizagem da matemática é um comportamento complexo dependente de variáveis individuais e culturais. Nesse sentido compreender quais mecanismo regulam tal aprendizagem é crucial para implementação de estratégias de ensino mais eficientes, assim como intervir no grupo de crianças com transtorno relacionado.

A discalculia do desenvolvimento é estudada há menos tempo quando comparada a outros transtornos de aprendizagem, como a dislexia. Hoje sabe-se que a aprendizagem da matemática depende de mecanismos cognitivos específicos e gerais. O senso numérico, o domínio específico da matemática, vem sendo investigado ostensivamente nos últimos 20 anos e, apesar das evidências sobre a associação dessas habilidades com o desempenho aritmético (Chen & Li, 2014; Fazio et al., 2014), sua utilidade do ponto de vista clínico não foi completamente elucidada (Júlio-Costa et al., 2015). Dentre outras limitações encontradas na transposição das evidências de pesquisa para a aplicação clínica, os critérios diagnósticos também têm um destaque.

Qualquer diagnóstico de transtorno de aprendizagem envolve uma avaliação da inteligência, porém uma das questões em debate diz respeito ao critério da discrepância. A maioria das pesquisas na área, assim como a nossa, mostra que a inteligência não é fator decisivo para o perfil de dificuldades das crianças. Tais argumentos têm subsidiado inclusive a proposta do principal manual diagnóstico de transtornos mentais (APA, 2013).

Existe uma linha de argumentação que busca desacreditar a relevância da inteligência para as dificuldades de aprendizagem (Sternberg & Grigorenko, 2002; Dennis et al., 2009), tanto no que diz respeito ao seu papel nos critérios diagnósticos (critério da discrepância), quanto na sua influência na caracterização do perfil cognitivo. Por outro lado, é inviável pensar em uma utilização irrestrita do critério de discrepância, por considerar que há sérias implicações psicossociais na limitação de recurso psicopedagógicos para um grupo de crianças com inteligência baixa e que também necessita de suporte extra, em virtude das dificuldades. Tal ponto é mais relevante no Brasil. Adicionalmente, há um grande número de evidências que

mostram a importância da inteligência como preditora isolada de desfechos (Hunt, 2010), incluindo o desempenho escolar (Deary & Johnson, 2010; Asbury & Plomin, 2013).

Por outro lado, não é possível simplesmente desconsiderarmos a inteligência, sabendo do seu papel na resposta à intervenção e no prognóstico das crianças (Deary & Johnson, 2010). Assim, com base nos dados da literatura e nas novas evidências levantadas pela presente tese, entende-se que uma posição mais complementar deve ser ponderada, no qual a inteligência não pode ser entendida como crucial para o diagnóstico, mas sim necessária para a construção do perfil e proposta de estratégias.

Apesar dos desfechos desfavoráveis tanto para o indivíduo quanto para sua família e até mesmo para o país (se pensarmos em termos de capital mental), pouco se sabe sobre as bases genéticas do transtorno de aprendizagem da matemática. Os estudos da presente tese indicam que mecanismos regulatórios das vias dopaminérgicos podem estar envolvidos na manifestação dos sintomas da discalculia, influenciando fatores subjacentes como memória operacional e ansiedade matemática. A despeito da natureza exploratória dos presentes estudos entende-se que há apontamentos de associações e um direcionamento para futuros estudos em relação análises e controle de variáveis. Estudos mais confirmatórios devem considerar informações na maior quantidade de níveis possíveis ao mesmo tempo (genético, molecular, cerebral, cognitivo). Novas pesquisas devem ainda ser realizadas com o intuito de confirmar os resultados aqui demonstrados. Entretanto para produção de dados mais conclusivo, torna-se necessário que estudos futuros restrinjam a faixa etária utilizada. A infância é uma fase em que acontecem rápidas modificações no cérebro dos indivíduos e uma amostra com idades mais próximas evita interferências de variáveis do desenvolvimento. Além disso, pesquisas com crianças com o transtorno de aprendizagem na matemática devem ajudar a esclarecer se os genes da COMT e DAT podem ser candidatos a marcadores biológicos. Descobertas nesse sentido ainda são muito escassas na literatura e podem auxiliar na validação nosológica do transtorno. O uso de medidas mais refinadas deve ser priorizado no sentido tanto de gerar dados mais coesos para realização de análises mais robustas, quanto para investigar efeitos diretos, mas também para mediação e moderação.

As principais inovações da tese dizem respeito à operacionalização da validade do critério de discrepância em crianças com dificuldades de aprendizagem na matemática. Além disso, procurou-se, com este trabalho, investigar o papel da inteligência no perfil cognitivo de

indivíduos com dificuldades na disciplina. Por fim, os estudos experimentais com polimorfismos para populações infantis/adolescentes são inéditos na literatura, até onde pode-se constatar, na averiguação da associação do gene da COMT com ansiedade matemática e na investigação simultânea da associação dos genes da COMT e DAT1 da memória operacional.

Os resultados ainda não têm implicação direta na interface neurociências e educação e na clínica, entretanto, em uma visão otimista, podem ser considerados passos para a consolidação dos critérios diagnósticos e conhecimento das bases genéticas da aprendizagem da matemática.

6.1. Referências

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ANEXO I – Publicações em jornais científicos durante o período de doutorado:

Júlio-Costa, A., Starling-Alves, I., Lopes-Silva, J. B., Wood, G., & Haase, V. G. (2015). Stable measures of number sense accuracy in math learning disability: Is it time to proceed from basic science to clinical application?. PsyCh journal, 4(4), 218-225.

Júlio-Costa, A., Antunes, A. M., de Almeida Prado, A. C., Carvalho, M. R. S., & Haase, V. G. (2014). Association between COMT val158met polymorphism and working memory tasks in children and adolescents: a systematic review. Neurotransmitter, 2.

Piccolo, L. R., Giacomoni, C. H., Julio-Costa, A., Oliveira, S., Zbornik, J., Haase, V. G., & Salles, J. F. (2017). Reading Anxiety in L1: Reviewing the Concept. Early Childhood Education Journal, 45(4), 537-543.

de Almeida Gomides, M. R., Haase, V. G., Martins, G. A., Barbosa, D. C. B. P., & Júlio-Costa, A. (2016). Utilização de Técnicas de Manejo Comportamental e Neuropsicológicas para Intervenção dos Transtornos de Aprendizagem. Interação em Psicologia, 18(3).

Lopes-Silva, J. B., Moura, R., Júlio-Costa, A., Wood, G., Salles, J. F., & Haase, V. G. (2016). What is specific and what is shared between numbers and words?. Frontiers in psychology, 7.

Antunes, A. M., Júlio-Costa, A., & Haase, V. G. (2015). Variações cariotípicas na Síndrome de Turner: uma análise do fenótipo cognitivo. Gerais: Revista Interinstitucional de Psicologia, 8(2), 348-358.

Haase, V. G., Júlio-Costa, A., & Silva, J. B. L. (2015). Por que o construtivismo não funciona? Evolução, processamento de informação e aprendizagem escolar. Psicologia em Pesquisa, 9(1), 62-71.

Carvalho, M. R. S., Vianna, G., Oliveira, L. D. F. S., Costa, A. J., Pinheiro-Chagas, P., Sturzenecker, R., ... & Haase, V. G. (2014). Are 22q11. 2 distal deletions associated with math difficulties?. American Journal of Medical Genetics Part A, 164(9), 2256-2262.

Haase, V. G., Júlio-Costa, A., Lopes-Silva, J. B., Starling-Alves, I., Antunes, A. M., Pinheiro-Chagas, P., & Wood, G. (2014). Contributions from specific and general factors to unique deficits: two cases of mathematics learning difficulties. Frontiers in psychology, 5.

Lopes-Silva, J. B., Moura, R., Júlio-Costa, A., Haase, V. G., & Wood, G. (2014). Phonemic awareness as a pathway to number transcoding. Frontiers in psychology, 5.

ANEXO II – Parecer do Comitê de Ética

UNIVERSIDADE FEDERAL DE MINAS GERAIS

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Endofenótipos das dificuldades de aprendizagem da matemática
Pesquisador: Vitor Geraldi Haase
Área Temática:
Versão: 4
CAAE: 15070013.1.0000.5149
Instituição Proponente: PRO REITORIA DE PESQUISA
Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 1.160.705
Data da Relatoria: 30/06/2015

UNIVERSIDADE FEDERAL DE MINAS GERAIS

Considerações sobre os Termos de apresentação obrigatória:
Documentos apresentados: projeto de pesquisa formatado na plataforma Brasil e também em word; folha de rosto devidamente preenchida e assinada pelo Diretor da Faculdade de Filosofia e Ciências Humanas; parecer consubstanciado emitido pelo Departamento de Psicologia da Faculdade de Filosofia e Ciências Humanas; carta de anuência da Diretoria do Instituto de Educação de Minas Gerais; autorização do Biobanco de Materiais do LGHM (Laboratório de Genética Humana e Médica; Biobanco Termo de Consentimento Livre e Esclarecido;TALE; TCLE para os pais; TCLE para professores.

Recomendações:
Recomenda-se a aprovação da emenda ao projeto de pesquisa.

Conclusões ou Pendências e Lista de Inadequações:
Somos favoráveis à aprovação da emenda ao projeto " Endofenótipos das dificuldades de aprendizagem da matemática do Pesquisador Prof. Dr. Vitor Geraldi Haase, com a inclusão de do TCLE para os professores.

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

Considerações Finais a critério do CEP:
Diante do exposto, o Comitê de Ética em Pesquisa da UFMG/ COEP-UFMG, de acordo com as atribuições definidas na Resolução CNS nº 466 de 2012 e na Norma Operacional nº 001 de 2013 do CNS, manifesta-se pela aprovação da emenda proposta ao projeto de pesquisa.

Endereço: Av. Presidente Antônio Carlos,6627 2º Ad SI 2005
Bairro: Unidade Administrativa II **CEP:** 31.270-901
UF: MG **Município:** BELO HORIZONTE
Telefone: (31)3409-4592 **E-mail:** coep@prpq.ufmg.br