Association between Val158Met COMT polymorphism and working memory tasks in children and adolescents: a systematic review

Annelise Júlio-Costa ¹ ², Andressa Moreira Antunes ² ³, Ana Carolina de Almeida Prado ², Maria Raquel Santos Carvalho ⁴ ⁵, Vitor Geraldi Haase ¹ ² ³

¹Programa de Pós-graduação em Neurociências, Instituto de Ciências Biológicas, Universidade Federal de Minas Gerais, Brazil
²Laboratório de Neuropsicologia do Desenvolvimento, Faculdade de Filosofia e Ciências Humanas, Universidade Federal de Minas Gerais, Brazil
³Programa de Pós-Graduação em Saúde da Criança e do Adolescente, Faculdade de Medicina, Universidade Federal de Minas Gerais, Brazil
⁴Programa de Pós-graduação em Genética, Instituto de Ciências Biológicas, Universidade Federal de Minas Gerais, Brazil
⁵Departamento de Biologia Geral, Instituto de Ciências Biológicas, Universidade Federal de Minas Gerais

Correspondence: Annelise Júlio-Costa
E-mail: julio.annelise@gmail.com
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Physiological changes caused by COMT have been associated with different information processing profiles. The aim of this study is to investigate, by means of a literature review, if the COMT polymorphic types influence the performance of children and adolescents in working memory tasks. We investigated articles that compared behavioral measures of working memory between COMT genotypes. Fourteen articles were selected to be part of this review. Although only a minority of selected studies presented differences in working memory between polymorphisms, we may not affirm that there is not such difference since there is no consistency in the analysis of intervening variables related to the COMT influence on working memory. Futures studies should have better control of these variables.

Keywords: Catechol O-Methyltransferase; COMT; working memory; children


Introduction

Developmental disorders are complex conditions caused by both genetic and environmental factors, as well as, the interaction of these factors. This complexity renders the investigation of the etiology of the developmental disorders difficult. These disorders can be investigated by means of endophenotype [1], which are intermediate phenotypes [2], or, in other words, molecular, neural or cognitive characteristics that are in between the association of genotype and phenotype. This research field contributes to the identification of the genetic risk factors associated with complex clinical conditions [3].

Working memory is a cognitive endophenotype widely associated with developmental disorders, such as ADHD [4], autism [5], dyslexia [6] and dyscalculia [7]. Working memory is the limited cognitive capacity that allows the temporary storage and processing information [8]. It is a very influential concept in several areas and its more accepted model was proposed by Baddeley & Hitch [9]. In addition to being an important marker of developmental disorders, working
memory plays a fundamental role in many complex processes of cognition. Therefore, working memory impairments affect directly, for example, the performance in daily activities and even in school learning.

Baddeley & Hitch’s model assumes that working memory consists of three components: a central executive that manages all mental activity (selective attention, cognitive flexibility, plan selection and execution, resources allocation and evocation of information stored in long-term memory [10]). In addition to the central executive, the model proposed two slave systems: the phonological loop and the visuospatial sketchpad. The first one retains and processes information encoded in the verbal form (auditory or visual inputs), whereas the second one is specialized in visual and spatial codification referring to the identity and spatial relationships of objects [11]. Afterwards, a fourth component was included in the model, the episodic buffer, which is responsible for the integration of working memory information to those recalled from long-term memory [19].

The prefrontal cortex is the brain region which is most frequently associated with working memory, although other areas are also assumed to be influential [8, 12, 13]. The information processing component involved in memory tasks is associated, in the molecular aspects, to the neurotranspharmacological functioning of dopamine [14].

Dopamine is synthesized in the cytoplasm of neurons from tyrosine and subsequently stored in secretory vesicles for release into the synaptic cleft [15]. Once released, dopamine inactivation occurs in two main forms: (1) through the dopamine transporter protein (DAT) and (2) by the action catechol-O-methyltransf erase enzyme (COMT) [15]). In the brain, the main area of COMT activity is the prefrontal cortex, where the concentration of DAT is low, where approximately 60% the dopamine degradation is depends on the COMT activity [16]. To the other hand, COMT responds for less than 15% of dopamine metabolism in the parietal cortex and in the striatum [17].

A polymorphism in the COMT gene has been associated with different patterns of information processing in the population. This polymorphism causes the substitution of methionine for valine at the aminoacid 158 (Val158Met) [18]. It has been proposed that the According to Chen et al. [19], the Met158Met enzyme has a higher degradation rate than the Val158Val enzyme. Also according to these authors, the heterozygous enzyme (Val158Met) has an intermediate processivity.

In the last decade, much was discussed about how different patterns of information processing are related to physiological changes associated with the COMT polymorphism. Vijayraghavan, Wang, Birnbaum, Williams and Arnsten [20] demonstrated that dopamine receptors (D1) have an inverted U curve pattern of activation in tasks of working memory. In summary, the authors suggested that there is an optimum concentration of dopamine in the synaptic cleft for activation of its receptors and such evidence was corroborated by other studies (review Mier, Kirsch and Meyer-Lindenberg [21]). Since COMT polymorphism influences the bioavailability of this neurotransmitter, it also interferes with dopaminergic transmission during the performance of working memory tasks. The model of brain activation regarding dopamine concentration suggests that in adult samples (typically developing), the genotype Met158Met is related to an optimal concentration and, therefore, it is located near the apex of the curve, followed by genotypes Val158Met and Val158Val respectively [22].

Stein, Newman, Savitz and Ramesar [24], in a review, suggested that homozygous Met158Met individuals tend to have a more cautious style of information processing, focusing attention and working memory (worrier strategy). Homozygous Val158Val individuals usually present an approach-and-exploration of the environment style, which favors adaptation under stress and better emotional regulation (warrior strategy).

Initially, studies investigating the influence of COMT polymorphism on cognition were conducted on schizophrenic patients using the Wisconsin Card Sorting Test (WCST) [23-27]. For Dickinson and Elvevågv [14], investigating this specific sample seems obvious to test the hypothesis of the COMT influence on executive functions, because: 1) schizophrenic patients demonstrated consistent changes in the dorsolateral prefrontal cortex activation during the execution of the WCST; and 2) antipsychotic medication affects the physiological responses of prefrontal regions. The results of these studies confirmed the previously formulated hypothesis: the COMT methionine allele is related to a better performance on executive function tasks, such as working memory ones.

Other studies, with healthy or psychiatric samples [22, 28-31], obtained the similar results, demonstrating differences of performance between COMT genotypes using not only the WCST but also other paradigms, for example, n-back tasks. However, a meta-analysis questioned the validity of such data pointing to the small size effects of these differences or inconsistent results [32].

Although behavioral findings are controversial, another meta-analysis revealed an association between COMT
Table 1. Numbers of articles found per group of terms

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Note: Terms “working memory” and “children” were not combined, because our main aim was investigate the influence of COMT and the terms does not contribute to this.

In children, results on the relationship between COMT polymorphism and performance in working memory tasks are rather scarce. Similarly to research in adults, only few studies have been conducted with a clinical population (diagnosed with ADHD) which have a behavioral phenotype of deficits in working memory and changes in the activation of prefrontal brain regions[33-35]. Behavioral data from these ADHD studies, unlike the results found in typical adult samples, do not suggest that Met158Met individuals[36,37] present a better performance. This may be indicative that the differences between COMT polymorphisms only emerge in individuals older than 10 years old. In view of the inconsistency in the literature, our aim is to investigate, by means of a systematic literature review, if the COMT polymorphisms are associated with differences on working memory tasks performance in children and adolescents.

Methods

We searched articles in two databases (Lilacs e PubMed) using the terms “Working memory”, “Catechol-O-Methyltransferase”, “COMT” and “Children”. The search terms were combined in groups: 1) "catechol-O-methyltransferase" and "children"; 2) "COMT" and "children"; 3) "catechol-O-methyltransferase" and "working memory"; 4) "COMT" and "working memory"; 5) "catechol-O-methyltransferase", "children" and "working memory"; and, 6) "COMT", "children" and "working memory". In the Table 1, the number of articles found per group of terms is shown.

All articles in English, Spanish or Portuguese published until August 2014 were included in this review. The inclusion criteria were: 1) experimental or quasi-experimental studies, 2) working memory measures explicitly defined by authors, 3) sample aged from 6 to 18 years old and 4) no intellectual disability.

Results

Initially, we screened the abstracts and excluded 11 articles which samples were composed by persons with 2q11.2 (subjects with a single copy of the COMT gene), 6 reviews and 143 studies that did not fulfilled the inclusion criteria. At first, we have selected 25 articles. However, we further excluded six studies that used only Continuous Performance Task (CPT) as a neuropsychological measure. This task is usually described as an attention measure [38, 39], which does not fulfill the inclusion criteria of having explicit working memory tasks. Furthermore, we also rejected two longitudinal studies [40, 41] that presented the same sample of a previous cross-section study [42] which was included in our sample. Therefore, fourteen articles were included in this systematic review.

In the Table 2, summary of the data of each selected study is presented. The oldest studies were published in 2004. The majority of them was from Europe (50%); other studies were from North America (35.7%), South American (7.1%) and Oceania (7.1%).

Fifty percent of the selected studies showed a mean age of their sample of 10 years old. With the exception of studies of Barnett et al. [42] and Wardle et al. [43], all of the others presented samples with a considerable age heterogeneity, with age ranges of, at least, 4 years. Another important sample feature regards neuropsychiatric diagnosis. In five of the fourteen studies (35.7%), the samples were composed of individuals with Attention Deficit and Hyperactivity Disorder (ADHD) [33-35, 44, 45]. In addition, in one study, part of the sample was constituted of psychotic individuals [46]. At last, authors subdivide differently the groups of COMT genotypes, twelve studies consider the three genotypes...
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(Val/Val vs. Val/Met vs. Met/Met). The other studies assume methionine as the dominant allele and divide the sample into two groups (Val/Val vs. Met+).

The aim of all studies was to investigate if the performance on working memory tasks was associated with the COMT genotype. Five articles found significant differences between genotype groups (Table 2). The group with the Met/Met genotype showed a better performance in three studies. A better performance of the group with the Val/Met genotype was found by Wahlstrom et al. [56] and Howarth et al. [49]. However, the results from Dumontheil et al. [37] indicated that a superior performance of the group with the Met/Met genotype could be observed only in individuals older than 10 years old. Additionally, Barnett et al. [42] found that the size effect of this difference was stronger in males. There were no differences between the genotypes in clinical samples, while it was observed neuropsychiatric symptoms. Nevertheless, in the study with a neurologic sample (brain tumor) the Val/Met

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genotype group showed a better performance in a Self-ordered search verbal task.

Different paradigms to evaluate working memory were used in the studies, such as span tasks [35, 36, 47], and n-back tasks [43], for instance. Finally, regarding statistical analyzes, two studies used non-parametric tests [44, 48]. The other studies used parametric tests, as follows: multivariate analysis [43, 45, 46] and bivariate analysis [33-37, 42, 47, 50].

Some of the selected articles contained other neuropsychological measures besides working memory, for example attention and short-term memory. However, none of these other measures was explored here because they are out of the scope of the present review.

Discussion

Here we describe the results of a systematic review of the literature examining the influence of COMT polymorphism on working memory performance of children and adolescents. The results point to data inconsistency, due to: the small number of studies, the wide age range of the samples, the number of genotype classes created (three, implying codominance and, or two, implying dominance), the variety of working memory paradigms and statistical analysis used. In the following section, we will discuss the results in further detail.

The advance of research on the association between COMT polymorphism and working memory performance is rather recent (from the early 2000s), but there are even less publications regarding children and adolescent samples. Furthermore, this is the first study that systematically reviews and organized the data obtained in this specific age, whereas for adults there is already available review studies [21, 32].

The wide variation in age of the samples is an important factor to be taken into account on children and adolescents studies. The maturation of cognitive skills occurs rapidly and performance can increase in a matter of few months, depending on age, particularly regarding executive functions, such as working memory [51]. In addition, the development of working memory is associated to frontal cortex maturation, which is known to be one of the last brain areas to develop in humans [13, 48].

It is also interesting that the working memory components do not develop linearly. For example, the phonological loop reaches its apex to seven years [52], while the central executive continues to develop until late adolescence [13, 48]. The most important gain regarding working memory development is the processing speed enhancement (better accuracy and automaticity), as well as the use of different strategies in problem solving [53].

Regarding the articles selected for this review, all studies had polymorphic groups matched by age (with the exception of Diamond et al. [48], on which all of the children were 6 years old). However, we need to compare the studies cautiously, since there is not a complete age overlap between the samples. Such discussion deserves attention, especially considering data presented by Dumontheil et al. [37]. These authors point out that the difference in group performance would emerge only after 10 years of age. Our results corroborate this finding: three articles, on which there were statistical differences between polymorphic groups, had sample with mean age around 10 years. The other study, which differences appeared in children younger than 10 years, had a small sample (Met/Met = 9; Val/Met = 16; Val/Val = 14) and used less robust statistical methods (nonparametric tests) [48]. Therefore, despite this study being a pioneer in the research field, it is necessary to interpret the results cautiously.

Three of the five articles that found differences in working memory performance suggest a superiority of the Met/Met genotype, as it was proposed by the Mattay et al. [22] model. This genotype would be in the apex of the "inverted U" curve in a chart showing the prefrontal cortex activation as a function of the dopaminergic concentration. However, Wahlstrom et al. [36] proposed from their own data that the best performance in adolescence is related to the heterozygous genotype, because in this phase of development there is a physiological increase of dopaminergic concentration. The physiological change causes a shift of each allele to right side of the curve. Thus, the heterozygous genotype place on the curve apex [36]. This suggestion is consistent with other maturation characteristics of adolescence, such as in impulsivity [54]. Furthermore, a study of children with brain tumor, treated with Conformal Radiation Therapy, the same results were found: better performance in the heterozygote group. In addition to the pathological differences between the two samples, there are only 120 individuals in both of them and new studies are needed to replicate the data.

Unlike the adults findings [25-27], there are no differences between genotype groups in children/adolescents with a neuropsychiatric disorder [33-35, 45]. This result indicates that neuropsychiatric disorders in children and adolescents may be more complex and that the environmental factors, for example, may have a greater impact than the variation of a single nucleotide base.

Regarding the stratification of the genotype groups, when we consider allele dominance, it is accepted that the
influence of one allele overlaps the other. However, in relation to the COMT gene, such dominance has not been demonstrated, there are only hypotheses for adult samples and children/adolescents. Thus, this organization of genetic information and groups division is a confounding variable for the interpretation of the results.

Additional difficulty in data interpretation is introduced by the use of tests based on different working memory models. Working memory as a construct is not yet fully established in the literature and its components can be measured by different sort of tasks. Tasks evaluating span (digits WISC, Corsi Blocks, e.g.) have a greater storage demand, while other tasks require more manipulation, e.g., n-back tasks; or even stronger behavior control, such as in self-ordered tasks. This engagement difference is associated with the recruitment of different prefrontal cortex circuits. Wardle et al. suggest that COMT may be more strongly associated to certain working memory tasks. There are different paradigms; it is difficult to consider whether they measured exactly the same working memory component.

Finally, we must emphasize the difference in the statistical analyzes. Parametric tests are more robust than the non-parametric ones, since they have more requirements regarding data distribution assumptions and they provide measures of confidence interval. Also, among the parametric analysis we can find those that used analysis of variance, regression analyzes or multivariate models. For this reason, the variables are tested in different ways, which does not allow a direct and homogeneous interpretation of the results.

Conclusion

Similarly to adult studies and meta-analyzes, the association between COMT polymorphism in children and adolescents performance in working memory is inconsistent. In adults, when we analyzed data from brain activation patterns instead of behavioral data, the results showed a superior performance related to the presence of the methionine allele. In children and adolescents, there is only one study with neuroimaging data available.

Although few articles have found differences between polymorphic groups, we can not affirm that data indicates complete lack of COMT influence, since we consider all variables raised by this review (age and neuropsychiatric sample characteristics, organization of genetic data, measure of working memory and statistical test).

New researches should aim at finding more consistent results, by trying not to investigate samples of both children and adolescents, and, instead, have a more homogeneous age range. Moreover, this research area needs to create its own investigation method, since the initial phase of human development differs greatly from adulthood. One important aspect of this developmental bias is that the relationship between COMT polymorphisms and working memory measures is inextricably linked to the maturation of the cortex prefrontal, which is the last brain region to develop.

Future studies must prioritize the use of a narrower age range in the samples and more refined working memory measures. Furthermore, clinical studies with other sort of populations, including ADHD children, will be useful in providing a better understanding of working memory deficits underlying developmental disorders, such as dyslexia and dyscalculia.

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Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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