

Cortical and subcortical polymorphisms: cognitive and motor implications

*Polimorfismos corticais e subcorticais:
implicações cognitivas e motoras*

*Polimorfismos corticales y subcorticales:
implicaciones cognitivas y motoras*

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Resumo

Introdução. A aprendizagem de habilidades motoras depende de processos cognitivos, com a memória operacional (MO) desempenhando papel central nos estágios iniciais. Esse processo envolve planejamento cognitivo no córtex pré-frontal dorsolateral, planejamento motor em áreas motoras secundárias e execução na área motora primária. A MO inclui armazenamento e processamento de informações via ativação neuronal, com participação do córtex pré-frontal (CPF), núcleos da base e hipocampo. Polimorfismos genéticos, como Val158Met (COMT), TaqIA (DRD2/ANKK1) e Val66Met (BDNF), influenciam a MO e a aprendizagem motora. **Método.** Este estudo revisou pesquisas sobre esses polimorfismos e suas implicações nas funções cognitivas e motoras, utilizando bases como PubMed, Scopus e *Web of Science*. **Resultados.** Enquanto alguns estudos identificaram associações entre genótipos e desempenho cognitivo/motor, outros foram inconclusivos, sugerindo que fatores genéticos e ambientais adicionais podem modular esses efeitos. Estudos que analisaram interações entre polimorfismos revelaram efeitos complexos, especialmente entre COMT e DRD2/ANKK1, dependendo do equilíbrio entre neurotransmissores e receptores em diferentes regiões encefálicas. Interações mais intensas foram observadas em alelos de alto desempenho. Compreender esses polimorfismos é essencial para esclarecer o funcionamento cerebral e suas interações, com impacto nas funções cognitivas e motoras, cruciais para o cotidiano. **Conclusão.** Estudos futuros devem considerar variáveis adicionais, como o tipo de tarefa e o tamanho da amostra, para aprofundar o conhecimento sobre os mecanismos das funções cognitivas e motoras.

Unitermos. Genética; COMT; DRD2; BDNF; Funções cognitivas; Funções motoras

Abstract

Introduction. Motor skill learning relies on cognitive processes, with working memory (WM) playing a central role in the early stages. This process involves cognitive planning in the dorsolateral prefrontal cortex, motor planning in secondary motor areas, and execution in the primary motor area. WM includes the storage and processing of information through neuronal activation, involving the prefrontal cortex (PFC), basal ganglia, and hippocampus. Genetic polymorphisms, such as Val158Met (COMT), TaqIA (DRD2/ANKK1), and Val66Met (BDNF), influence WM and motor learning. **Method.** This study reviewed research on these

polymorphisms and their implications for cognitive and motor functions, using databases such as PubMed, Scopus, and Web of Science. **Results.** While some studies identified associations between certain genotypes and cognitive/motor performance, others were inconclusive, suggesting that additional genetic and environmental factors may modulate these effects. Studies analyzing interactions between polymorphisms revealed complex effects, especially between COMT and DRD2/ANKK1, depending on the balance between neurotransmitters and receptors in different brain regions. Stronger interactions were observed in high-performance alleles. Understanding these polymorphisms is essential to clarify brain functioning and interactions, impacting cognitive and motor functions crucial for daily life. **Conclusion.** Future studies should consider additional variables, such as task type and sample size, to deepen the understanding of the mechanisms underlying cognitive and motor functions.

Keywords. Genetics; COMT; DRD2; BDNF; Cognitive functions; Motor functions

Resumen

Introducción. El aprendizaje de habilidades motoras depende de procesos cognitivos, con la memoria operativa (MO) desempeñando un papel central en las etapas iniciales. Este proceso implica planificación cognitiva en la corteza prefrontal dorsolateral, planificación motora en áreas motoras secundarias y ejecución en el área motora primaria. La MO incluye almacenamiento y procesamiento de información mediante la activación neuronal, con la participación de la corteza prefrontal (CPF), los núcleos basales y el hipocampo. Polimorfismos genéticos, como Val158Met (COMT), TaqIA (DRD2/ANKK1) y Val66Met (BDNF), influyen en la MO y el aprendizaje motor. **Método.** Este estudio revisó investigaciones sobre estos polimorfismos y sus implicaciones en las funciones cognitivas y motoras, utilizando bases de datos como PubMed, Scopus y Web of Science. **Resultados.** Mientras que algunos estudios identificaron asociaciones entre ciertos genotipos y el rendimiento cognitivo/motor, otros fueron inconclusos, sugiriendo que factores genéticos y ambientales adicionales pueden modular estos efectos. Los estudios que analizaron interacciones entre polimorfismos revelaron efectos complejos, especialmente entre COMT y DRD2/ANKK1, dependiendo del equilibrio entre neurotransmisores y receptores en diferentes regiones encefálicas. Se observaron interacciones más intensas en alelos de alto rendimiento. Comprender estos polimorfismos es esencial para aclarar el funcionamiento cerebral y sus interacciones, con impacto en las funciones cognitivas y motoras, cruciales para la vida cotidiana. **Conclusión.** Los estudios futuros deben considerar variables adicionales, como el tipo de tarea y el tamaño de la muestra, para profundizar en el conocimiento sobre los mecanismos de las funciones cognitivas y motoras.

Palabras clave. Genética; COMT; DRD2; BDNF; Funciones cognitivas; Funciones motoras

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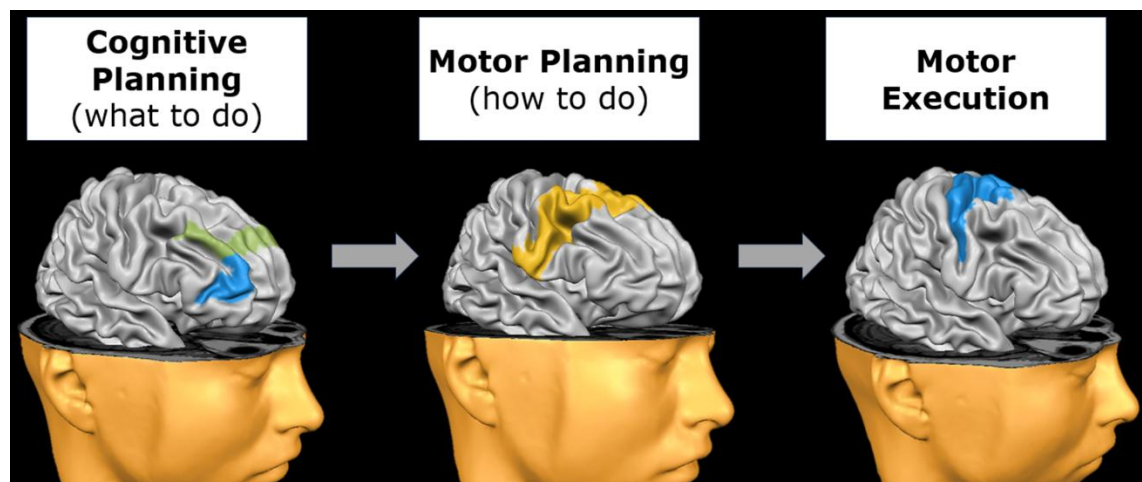
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INTRODUCTION

Various cognitive processes are involved in motor skill learning. In particular, behavioral and neural evidence suggests that working memory (WM) plays a crucial role in motor skill learning, especially in the early stages¹⁻³. This relationship indicates the presence of prior cognitive planning (e.g., dorsolateral prefrontal cortex), followed by

motor planning (e.g., secondary motor areas), and finally motor execution (e.g., primary motor area; Figure 1). WM is one of the core executive functions (EFs). EFs encompass a range of higher-order mental processes essential in situations requiring focus and attention, where acting automatically or relying on instinct or intuition would be inadvisable, insufficient, or unfeasible. There is general consensus that three main EFs form the foundation of these processes: WM, inhibitory control, and cognitive flexibility. From these fundamental EFs, higher-order EFs develop, such as reasoning, problem-solving, and planning⁴ (Figure 2).

Figure 1. Cortical Areas and Functions. From left to right – dorsolateral prefrontal cortex, secondary motor areas, and primary motor area.

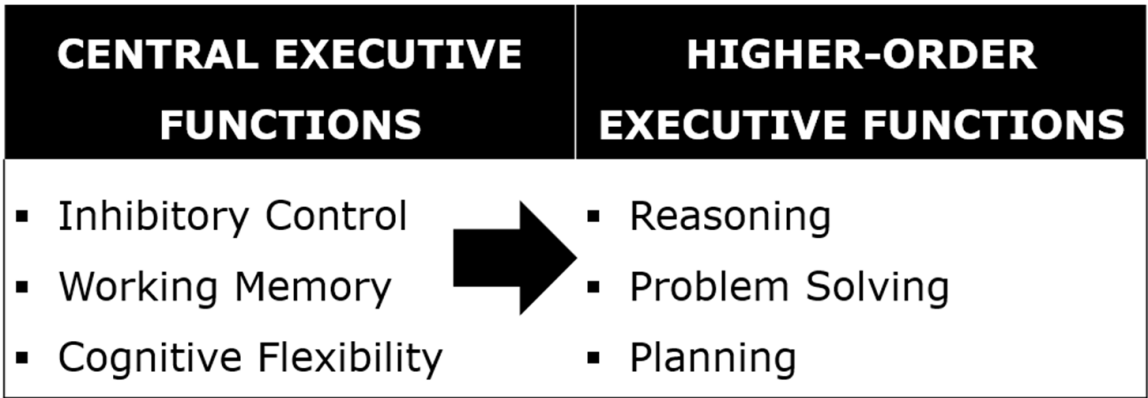


Source: The authors.

WM is a cognitive system that involves both the active storage and processing of information, enabling the execution of specific tasks or behaviors. From a neural

perspective, WM can be understood as the maintenance and updating of information encoded in the active firing of neurons⁵ and comprises three main components: maintenance, manipulation, and inhibition of task-irrelevant information⁶. This EF is essential for understanding any process that unfolds over time, as it requires keeping in memory what has occurred and relating it to what is yet to come. This is crucial for making sense of written or spoken language, performing mental math, mentally reorganizing items (such as a shopping list), translating instructions into action plans, updating information, considering alternatives, and mentally relating information to derive a general principle or identify relationships between items or ideas⁴. WM has been widely studied using neuroimaging techniques, investigations in individuals with brain lesions, brain stimulation, and behavioral tasks in healthy individuals⁷.

Figure 2. Executive Functions.



Regarding the mechanisms and brain structures involved in WM, numerous experimental studies have been conducted⁸, and computational models have been formulated⁵. Individuals who had suffered a stroke were investigated and it was found that lesions in the left basal ganglia made WM more susceptible to irrelevant information⁸. In contrast, lesions in the right PFC impaired the ability to retain more than a few items in WM. These findings support theoretical models that involve the participation of the PFC and basal ganglia in WM, suggesting that the basal ganglia act as a "gate", allowing only relevant information to be forwarded to the PFC, where it is actively maintained in WM. According to the computational model proposed by Frank⁵, two brain structures play crucial roles in WM. Specifically, WM functions in the frontal cortex depend on the idea that the basal ganglia are essential for initiating the storage of new memories. In other words, the disinhibition of thalamo-cortical loops by the basal ganglia results in the opening of the "gate" to WM, allowing rapid updating of information. Conversely, when the thalamo-cortical loops are inhibited, the "gate" remains closed, enabling the frontal cortex to maintain already stored information. This active gating mechanism dynamically regulates the influence of stimuli on the WM system. When the gate is open, stimulus information can flow strongly into the WM system, facilitating rapid updating. When the gate is closed, stimuli exert less influence on WM, allowing robust maintenance of information even during continuous

processing. This model is based on the general function of the basal ganglia in the frontal cortex, which is to "release the brakes" for motor actions and other functions⁵. Thus, the underlying principle of the mechanism by which the striatum selects representations for WM updating, abstract rule learning, and attentional shifting may be similar to what is observed in procedural learning⁹.

Various factors can influence WM and, consequently, motor skill learning¹⁻³. Advances in molecular genetics have significantly contributed to the investigation of the underlying mechanisms of WM by exploring individual genetic content. The main focus has been on genes that modulate dopamine (DA) levels, a neurotransmitter crucial for WM. Specifically, scientific literature has examined the effects of two single nucleotide polymorphisms (SNPs), common in the general population, that affect dopaminergic activity: the Val158Met polymorphism of the catechol-O-methyltransferase (COMT) gene and the TaqIA polymorphism of the DRD2/ANKK1 gene. DA levels in the PFC are influenced by the Val158Met polymorphism of the COMT gene. Parallely, there is an extensive body of literature investigating genes that influence striatal DA, due to the strong cortico-striatal connections and evidence supporting the striatum's role in EFs like WM. Although the striatum is classically associated with procedural learning, it also plays a role in updating WM content. In this context, DA D2 receptors, which are abundant in the striatum, have their density influenced by the TaqIA polymorphism of the

DRD2/ANKK1 gene. At the same time, the Val158Met polymorphism of the COMT gene determines DA levels in the PFC and has no significant influence in the striatum, where D2 receptors predominate⁷. The aim of this narrative review was to compile publications on polymorphisms in genes associated with the PFC and basal ganglia, as well as their implications for cognitive and motor functions. Additionally, in the final section, publications that explored polymorphisms related to the hippocampus, such as the BDNF gene, will be discussed.

METHOD

To compile the relevant literature on the interaction of polymorphisms in genes related to the prefrontal cortex (Val158Met - COMT), basal ganglia (TaqIA - DRD2/ANKK1), and hippocampus (Val66Met - BDNF), and their implications for cognitive and motor functions, a narrative review was conducted. This method is widely recognized as fundamental to scientific production¹⁰, being used to describe and discuss the development or the “state of the art” of a given topic from a theoretical or conceptual perspective¹¹. Narrative reviews allow the author to interpret and critically analyze the existing literature.

For this review, searches were conducted in the PubMed/MEDLINE, Scopus, and Web of Science – Core Collection databases. The search was limited to articles in English, published between 2004 and 2024, and selection was based on a critical reading of the material found.

Additionally, the reference lists of the selected articles were reviewed to identify relevant studies that had not been captured in electronic searches.

The exclusion criteria included studies that did not directly address the relationship between the mentioned polymorphisms and cognitive and motor functions or their interaction, as well as articles that did not present a clear methodology.

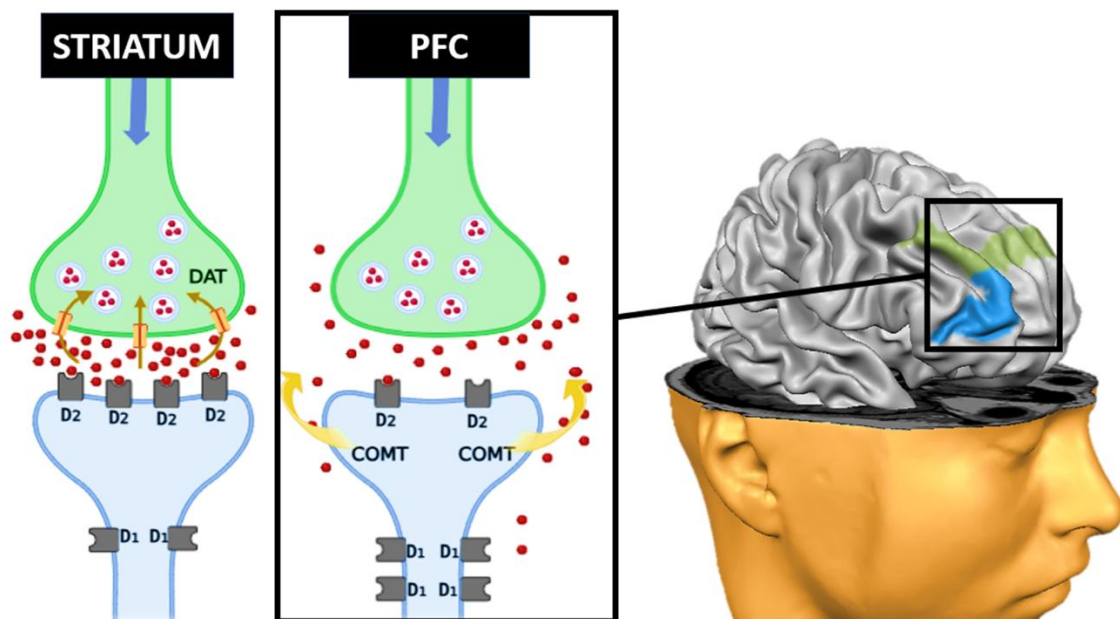
RESULTS AND DISCUSSION

COMT enzyme, COMT gene, Val158Met polymorphism of the COMT gene (RS4680) and PFC

The COMT enzyme is widely expressed throughout the brain and plays a crucial role, especially in controlling DA levels in the PFC, being responsible for over 60% of its metabolic degradation^{12,13}. In subcortical systems, DA is mainly regulated by rapid reuptake via the dopamine transporter (DAT). However, the PFC exhibits lower DAT expression, resulting in a higher amount of extracellular DA compared to the striatum. This allows DA to diffuse over longer distances, acting on extrasynaptic D1 receptors (Figure 3).

COMT enzymatic activity distinctly influences DA transmission in the PFC (mesocortical dopaminergic system) and the nucleus accumbens (mesolimbic dopaminergic system).

Figure 3. Dopaminergic Transmission in the Prefrontal Cortex (PFC) and Striatum. In the striatum, the dopamine transporter (DAT) is responsible for removing dopamine from the synaptic cleft, with catechol-O-methyltransferase (COMT) playing at most a minor role. In the PFC, the absence of DAT at the synapse means that COMT plays a more prominent role in dopamine inactivation.



Source: The authors.

In the PFC, DA transmission is regulated by dopaminergic neurons from the ventral tegmental area (VTA), which release high concentrations of DA into the synaptic cleft, allowing it to diffuse beyond the cleft and stimulate nearby extrasynaptic sites. This differs from the mesolimbic system, where phasic DA transmission is more restricted to the synaptic cleft¹⁴.

In the nucleus accumbens, extracellular DA at low and constant levels is known as tonic DA. This tonic release is driven by the slow and irregular activity of dopaminergic neurons from the VTA, resulting in low levels of DA in the extrasynaptic space, where it is degraded by the COMT enzyme. In contrast, phasic DA transmission occurs with the

intense activation of VTA neurons, releasing large amounts of DA into the synaptic cleft, where it binds to postsynaptic D2 receptors. Phasic DA is rapidly inactivated by DAT before diffusing from the synaptic cleft, making it less susceptible to COMT action. While tonic DA concentrations are too low to activate postsynaptic D2 receptors, they are sufficient to stimulate presynaptic D2 autoreceptors, which inhibit phasic DA release. Therefore, tonic DA levels, regulated by COMT, have a modulatory effect, reducing phasic DA release¹⁴. The activity of the COMT enzyme, which distinctly affects DA transmission in the PFC and nucleus accumbens, can be influenced by the Val158Met single nucleotide polymorphism (SNP) of the COMT gene (rs4680), resulting in variations in the enzyme's thermostability and, consequently, its activity.

The COMT gene is located on chromosome 22, band q11.2. COMT enzyme activity in human populations presents a trimodal distribution due to the presence of the functional Val158Met polymorphism (rs4680) in the gene's coding sequence. This polymorphism involves the substitution of guanine (G) for adenine (A), resulting in the replacement of the amino acid valine (Val) with methionine (Met) at position 158 of MB-COMT¹⁵. Individuals homozygous for the Met allele exhibit low enzymatic activity, with a three- to four-fold reduction in COMT activity compared to individuals homozygous for the Val allele, leading to greater synaptic DA availability. On the other hand, individuals homozygous for the Val allele display high enzymatic activity, resulting in lower synaptic DA availability¹⁴⁻¹⁶. Since the alleles are

codominant, Val/Met heterozygotes demonstrate intermediate levels of COMT activity and DA availability^{14,15}.

The Val158Met polymorphism of the COMT gene has been extensively studied in relation to cognitive/executive and motor functions, both in clinical and non-clinical samples^{6,7,16-21}. An interesting point that has been investigated is the relationship between the differential effects of COMT genotypes and EFs mediated by the PFC. For example, individuals homozygous for the Met allele exhibit greater efficiency and better performance in executive function components that require stable information maintenance. Conversely, individuals homozygous for the Val allele exhibit greater efficiency when cognitive flexibility is needed, such as during task switching or rapid updating of information¹⁶. Based on the above, a question arises: are these theoretical speculations congruent with the existing data in the literature that relate COMT genotypes to cognitive performance?

Regarding studies on cognitive/EFs, it was analyzed twenty-six studies that investigated the COMT gene polymorphism and its associations with cognitive/EFs in clinical and non-clinical samples²¹. Of these studies, except for two, it was indicated that individuals homozygous for the Met allele tend to perform better in tasks involving a WM component²¹. However, some studies did not find such an association. For example, in the meta-analysis¹⁷ which evaluated associations between COMT gene polymorphism and measures of memory and EFs, no consistent association

was observed between COMT genotypes and most phenotypes. The authors concluded that, despite initially promising results, the COMT gene polymorphism appears to have a limited or non-existent association with cognitive/EFs¹⁷. Regarding studies on motor functions, studies also revealed inconsistencies in the differential effects of COMT gene genotypes^{19,20}. These studies do not confirm the theoretical speculations presented earlier, both for cognitive and motor functions. These inconclusive findings suggest a still-limited understanding of the effects of COMT gene genotypes on cognitive and motor performance. Possible reasons for these inconsistencies include the use of different types of tasks, the need for larger samples, and, perhaps more significantly, the influence of still-unknown interactions with other genes in various regions of the brain^{7,19}.

Effects of the interaction of COMT and DRD2 gene polymorphisms on cognitive and motor functions

The inconsistent findings regarding the effects of COMT gene genotypes on cognitive performance indicate an incomplete understanding, possibly due to the lack of investigation into unknown interactions with other genes in different brain regions. Moreover, considering that cortico-striatal dopaminergic pathways modulate WM performance, it makes sense to simultaneously investigate polymorphisms in the COMT and DRD2 genes. Several reasons exist to examine the interaction between these genes: (1) COMT

gene genotypes affect the activation rate of D1 and D2 receptors, suggesting that functional polymorphisms in these two receptor genes may also influence population variation in cognitive performance. Pharmacological studies have demonstrated that EFs, such as WM, are modulated by functional variation in both receptors. However, the research has been more in-depth, focusing on the ANKK1-Taq1A polymorphism of the DRD2 gene²¹; (2) the DRD2 gene encodes the DA D2 receptor, which is predominantly expressed in the striatum²². There are strong cortico-striatal connections and evidence that the striatum plays a role in EFs. The PFC interacts with the striatum in cortico-striatal circuits that are partially segregated and interactive^{23,24}.

The DRD2 gene is approximately 270 kB in length and contains eight exons²⁵. The most frequently studied polymorphism associated with this gene is the Taq1A restriction fragment length polymorphism (rs1800497), located in the Taq1A locus in the 3' untranslated region of the gene^{25,26}. This polymorphism is related to a reduction in the density of the DA D2 receptor²⁶. Taq1A is situated 10 kb downstream of the DRD2 and may be in a different coding region or in a regulatory region of the gene²⁶. In this downstream region, a new kinase gene has been identified, referred to as ankyrin repeat and kinase domain containing 1 (ANKK1). The relationship between the Taq1A polymorphism of the DRD2/ANKK1 gene and D2 receptor binding levels in healthy individuals was investigated²⁷. D2 receptor binding was measured by autoradiography in the

caudate nucleus, putamen, and nucleus accumbens, using the specific D2 receptor ligand ([3H] -raclopride). The results indicated that the presence of one or two A1 alleles was associated with a reduction in D2 receptor binding in all regions of the striatum, with statistically significant findings observed in the ventral caudate and putamen. More specifically, a statistically significant reduction of 30-40% in D2 receptor binding in the striatum was observed in individuals with one A1 allele compared to those homozygous for the A2 allele²⁷. Subsequent studies demonstrated that individuals with genotypes associated with reduced D2 receptor density, such as the A1/A1 genotype, show declines in cognitive processing and motor performance, as well as inferior motor learning^{28,29}.

Regarding studies on cognitive/EFs, the interaction between the COMT and DRD2 gene polymorphisms contributes to individual differences in WM⁶. The study investigated whether optimal performance in different components of WM, such as maintenance, manipulation, and inhibition of irrelevant information, is related to the interaction between DA availability in the PFC and D2 receptor density in healthy adults. The results showed that the Val158Met polymorphism of the COMT gene is modulated by the TaqIA polymorphism of the DRD2/ANKK1 gene. Better performance in WM in the Val- group, presumably with high prefrontal DA levels, was observed only when D2 receptor density was high (e.g., in the A1- group). These findings suggest that the balance between neurotransmitter

availability and receptor density contributes to optimal WM performance. In summary, both an enzyme that catabolizes DA slowly and a high concentration of DA receptors have been associated with good WM performance. Thus, these polymorphisms may interact to producing differentiated behavioral phenotypes.

Further complementing the results of the previously mentioned study, it was investigated the interaction between the COMT gene polymorphism (Val allele) and the DRD2/ANKK1 gene polymorphism (A1 allele) in cognitive performance, as measured by the Trail-Making Test³⁰. The results showed a significant interaction between task complexity and genotype in the more demanding condition (Trail B), with the worst performance observed in the Val+/A1+ group. These findings suggest that both a fast-acting DA catabolizing enzyme and a low concentration of DA receptors are associated with poorer executive function performance. In the study, the authors examined the effects of COMT and DRD2/ANKK1 polymorphisms on WM performance⁷. The results indicated that the presence of the Val allele could negatively impact WM in different ways: in the A1- group, it tended to increase reaction time, while in the A1+ group, it tended to reduce accuracy. However, it is important to emphasize that these effects were only trends.

Subsequent studies, such as that of Garcia-Garcia¹⁸, provided additional and expanded insights into Stelzel⁶. They investigated the interaction between the two polymorphisms and their effects on the neural mechanisms involved in task

set switching¹⁸. The results revealed a significant interaction between these two genes, evidenced by specific behavioral costs and an increase in the nP3 component, reflecting the mechanisms of task set updating. This effect was observed only in individuals who maintained a balance between DA concentrations and receptor density (i.e., Met/A1- and Val/A1+). Conversely, individuals with a “dysbalance” (i.e., Met/A1+ and Val/A1-) exhibited enhanced nP3 responses to all sensory changes, indicating task set updating that appears to be independent of task context. These findings suggest that a balance between neurotransmitter concentrations and receptor density may be crucial for optimizing both the active maintenance of representations and the flexible updating of those representations in response to contextual task demands^{9,18}.

The role of alleles from genes involved in dopaminergic transmission (COMT and DRD2) was investigated as indicators of individual differences in motor sequence learning and visuomotor adaptation²⁹. The main hypothesis was that individuals homozygous for the Met allele (COMT) and the G allele (DRD2), associated with a higher density of D2 receptors, would exhibit higher rates of motor learning. The results indicated that, for the motor sequence learning task, the Val/Val group performed worse compared to the Met/Met group. Additionally, the TT group performed worse than the GT group. The authors suggested that for this task, the genotypes of the COMT and DRD2 genes could influence motor performance but not necessarily motor learning.

However, the experiment was conducted in a single session and did not include learning assessments such as retention or transfer. Regarding the additive effects of high-performance alleles (HPAs) from the two genes, the main effect of HPAs was identified on overall reaction time. Individuals with only one HPA exhibited slower reaction times and higher error rates compared to those with two, three, or four HPAs in the motor sequence learning task. In the visuomotor adaptation task, carriers of one HPA made more directional errors than those with three or four HPAs, and carriers of two HPAs made more errors compared to those with four HPAs.

The research was expanded to include older adults and the brain-derived neurotrophic factor (BDNF), in addition to the COMT and DRD2 genes³¹. BDNF plays a crucial role in neuroplasticity and is indirectly involved in dopaminergic function. The authors sought to investigate whether performance and motor learning in young and older adults were associated with age and the genotypes of the COMT, DRD2, and BDNF genes. A polygenic approach was adopted, creating a score that reflected the number of alleles considered high performing (i.e., alleles previously associated with better performance in cognitive and motor tasks). The results indicated that in the motor sequence learning task, the HPA score influenced performance only in older adults, with higher scores associated with poorer performance. Conversely, in the visuomotor adaptation task, the effect of the HPA score was observed only among young

adults, with higher scores associated with better performance. The study did not include learning assessments, similar to the one conducted in 2014²⁹.

It is crucial to investigate learning through specific tests, as memory consolidation depends on the stabilization of behavior. The molecular processes of memory consolidation manifest clearly and effectively when this behavioral stabilization occurs. For example, if an individual exhibits a faster learning rate during the initial phase of learning, which is dependent on cognitive processes, they may have more time to stabilize behavior during the slower phase of learning. This extended stabilization time may be associated with better consolidation, as reflected in learning tests. Individuals who have a prolonged slow learning phase tend to perform better on these tests, as this period, which occurs at the end of learning, is crucial for memory consolidation and involves various molecular processes, such as long-term potentiation (LTP). An example of this can be seen in the study which investigated the association between the expression of the alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor and states of fast learning and slow learning³². The results showed that varied practice of a motor task, compared to constant practice, was more associated with the N-Methyl-D-Aspartate (NMDA) receptor and exhibited higher expression of AMPA receptors. This increased expression of AMPA was associated with the slow learning state, suggesting that the molecular processes

involved in synaptic strengthening, such as increased synaptic weight, are fundamental for memory formation.

Information related to the aim, sample, genotype and group distribution, task types, results, and discussion of the studies mentioned in this section can be found in Table 1.

Table 1. Information on the studies analyzed in the section on the effects of genetic polymorphisms of the COMT and DRD2/ANKK1 genes on cognitive/executive and motor functions.

STUDY	AIM	SAMPLE	DISTRIBUTIONS AND GROUPS	TASK TYPES	RESULTS AND DISCUSSION
Stelzel ⁶	To examine how the COMT Val158Met / DRD2/ANKK1-TaqIa epistasis affects three basic component processes of WM, namely, the maintenance of information in WM, manipulation of WM contents, and inhibition of task-irrelevant information.	296 healthy caucasian participants; 142 men (23.0±2.64 years); 154 women (22.64±2.56 years).	Val+ / A1- =140; Val+ / A1+ =77; Val- / A1- =52; Val- / A1+ =27.	Cognitive - WAIS-III digit span forward and BIS memory scale: WM maintenance; - WAIS-III digit span backward, letter number sequencing: WM manipulation; - Operation span, listening span, counting span. The following three tasks with a similar design were used. Participants were required to store and reproduce a set of letters or numbers, alternating this activity with a secondary task, such as solving equations (operation span), evaluating sentences (listening span), or counting shapes (counting span): WM inhibition.	- The Val158Met polymorphism of the COMT gene is modulated by the TaqIA polymorphism of the DRD2/ANKK1 gene; - The best performance in WM was observed in the Val- group, associated with presumably high prefrontal DA levels, but only when D2 receptor density was high (e.g., the A1- group); - Findings suggest that the balance between neurotransmitters and receptors contributes to optimal performance in WM; - The Val+/A1+ group performed better on the manipulation component of WM, though interindividual variability prevented statistical significance; - This effect was only observed in the manipulation component, with no impact on the maintenance or inhibition components.
Garcia-Garcia ¹⁸	To examine the interaction between two polymorphic variations of genes involved in regulating prefrontal and striatal DA (COMT and ANKK1) in the neural mechanisms of task-set switching.	35 healthy caucasian participants (6 men, 2 left-handed, 22±4.2 years, age range 18-29 years).	Val+ / A1- = 12 (1 man); Val+ / A1+ = 8 (2 man); Val- / A1- = 9 (3 men); Val- / A1+ = 6.	Cognitive - A task-cueing protocol, inspired by the WCST and adapted for ERP measurement, was used. Each trial included a tonal cue followed by a display with four key cards and one choice card. Participants matched the choice card based on color or shape, determined by the tonal cue (500/1000 Hz for color, 2000/4000 Hz for shape). - The design independently manipulated cue-switches (sensory change) and task-switches (rule change), with three trial types: repeat (same cue and task), cue-switch (cue change, same task), and task-switch (both change). Tone-task associations were counterbalanced, and stimuli were presented using Presentation® software. Participants responded using a keyboard, and trials were randomized across 200 experimental and 50 practice trials. Timing varied, with cue-target intervals (650±150 ms) and response-cue intervals (1100±100 ms). Targets remained on-screen until response or for a maximum of 3000 ms.	- Interaction between the two genes, shown by specific behavioral costs and an increase in the amplitude of the nP3, which reflects task set updating mechanisms; - This effect was observed only in individuals with a balance between DA and receptor density (e.g., Val-/A1- and Val+/A1+); - Individuals with a "genetic imbalance" (e.g., Val-/A1+ and Val+/A1-) exhibited enhanced nP3* responses to sensory changes, indicating updates independent of the task context; - These findings suggest that the balance between neurotransmitters and receptors is crucial for the effective maintenance and updating of contextual representations.

Table 1 (cont.). Information on the studies analyzed in the section on the effects of genetic polymorphisms of the COMT and DRD2/ANKK1 genes on cognitive/executive and motor functions.

STUDY	AIM	SAMPLE	DISTRIBUTIONS AND GROUPS	TASK TYPES	RESULTS AND DISCUSSION
Wishart ³⁰	To examine the effects of the COMT Val158Met genotype on executive function in healthy adults, and to test for potential interacting effects of three common, well-studied genotype variations thought to influence cognition: APOE, BDNF, and ANKK1.	95 healthy caucasian participants (28 men, 67 women, age range 18–85 years).	Val+ / A1- = 49; Val+ / A1+ = 20; Val- / A1- = 12; Val- / A1+ = 14.	Cognitive TMT and DKEFS: TMT Part A and DKEFS Trial 2 require sequencing, psychomotor speed, and visuo-perceptual ability; TMT Part B and DKEFS Trial 4 make additional demands on cognitive flexibility and WM.	- There was a significant interaction between COMT and ANKK1 for Trails B; individuals with both the A1 allele of ANKK1 and the Val allele of COMT showed the lowest performance; - This interaction between COMT and ANKK1 suggests that genetic variations associated with central dopaminergic systems may act together, influencing individual differences in executive abilities.
Berryhill ⁷	To investigate the effects of the COMT (Val158Met) and DRD2/ANKK1 (TaqIa) gene polymorphisms on working memory performance in healthy adults.	134 participants (53 men, 81 women, 22.8±6 years, age range=18–57; aged 36–57: N=6, aged 26–35: N=25, aged 18–24: N=103).	Met/Met A1+ = 13; Val/Met A1+ = 28; Val/Val A1+ = 20; Met/Met A1- = 14; Val/Met A1- = 35; Val/Val A1- = 23.	Cognitive A WM task with sequentially presented color patches was used. Each stimulus was shown for 1000 ms, with non-primary colors chosen to minimize verbal strategies. Trials included either four or six stimuli, presented in a pseudorandom order. After a variable delay (1000 ms or 5000 ms), a probe item appeared, and participants indicated whether it had been shown earlier (chance = 50%). The task consisted of 104 trials, lasting about 15 minutes, with instructions to respond quickly and accurately.	- The results indicated that the COMT effect was more prominent in the A1- group, with Met/Met A1- homozygotes responding faster than both Val/Met A1- heterozygotes and Val/Val A1- homozygotes, showing a significant difference compared to the Val/Val A1- group. This finding provides some support for the idea of a possible interdependence between these two genes; - The accuracy data add complexity to the interpretation of these results. A marginally significant interaction indicated that behavioral patterns in the DRD2/ANKK1-TaqIa groups varied according to the COMT genotype. The Val allele benefited the A1- group but harmed the A1+ group. Thus, there were indications that the presence of the Val allele could negatively affect working memory performance in different ways: in the A1- group, it tended to increase reaction time, while in the A1+ group, it tended to reduce accuracy. However, these epistatic effects were not strong enough to produce significant gene × gene interactions and should, therefore, be interpreted with caution.

Table 1 (cont.). Information on the studies analyzed in the section on the effects of genetic polymorphisms of the COMT and DRD2/ANKK1 genes on cognitive/executive and motor functions.

STUDY	AIM	SAMPLE	DISTRIBUTIONS AND GROUPS	TASK TYPES	RESULTS AND DISCUSSION
Noohi ²⁹	To investigate the association between the dopaminergic system polymorphisms (COMT Val158Met and DRD2 G>T) and motor learning in women.	68 healthy caucasian female (european) participants (20±1.9 years).	COMT: Met/Met = 20; Val/Met = 35; Val/Val = 11; DRD2: GG = 45; GT = 22; TT = 3; Number of high-performance alleles: 1 = 8; 2 = 15; 3 = 30; 4 = 15.	Motor Sequential motor learning: The goal was to respond to visual stimuli presented on a computer screen by pressing the key that corresponded to the given stimulus as fast and as accurately as possible. The stimuli were presented following either a random or fixed sequence. Visuomotor adaptation: To manually control the movement of a cursor displayed on a monitor by using a joystick. The center of the screen was assigned as the starting point and the target (red circle) appeared randomly for 4 seconds either above, below, to the left or to the right of the starting point.	- HPA influenced reaction time in the motor sequence task but not the extent of learning. Individuals with only one HPA had slower responses and higher error rates compared to those with more HPAs; - The authors suggest that higher DA levels may be associated with performance but not necessarily with motor sequence learning. Additionally, they highlight that the definition of learning phases used is task-specific and not generalizable to other motor learning paradigms; - In the visuomotor adaptation task, there was a strong correlation between adaptation rate and the presence of three or four HPAs, indicating that these individuals exhibited more efficient motor adaptation. However, this relationship was not observed in motor sequence learning; - These findings support the hypothesis that genotypic effects are task-specific.
Noohi ³¹	To investigate the association between the COMT, DRD2 and BDNF polymorphisms and motor learning.	131 healthy caucasian female (european) participants; 68 young (21±1.9 years); 63 elderly (71±4.9 years).	Number of high-performance alleles: Young: 0 = 0*; 1 = 0*; 2 = 4; 3 = 13; 4 = 13; 5 = 25; 6 = 13; Elderly: 0 = 1*; 1 = 1*; 2 = 5; 3 = 13; 4 = 19; 5 = 17; 6 = 7;	Motor Sequential motor learning: Same as Noohi et al. (2014); Visuomotor adaptation: Same as Noohi et al. (2014); Grooved Pegboard Test: Participants were instructed to pick up one peg at a time from the peg pool and place it in the holes as fast as possible. Pegs needed to be rotated between the thumb and the index finger to fit the alignment of the holes.	- The results showed an association between the COMT Val158Met polymorphism and motor behavior; Several associations were found between genetic profiles (COMT, DRD2, BDNF polymorphisms), motor performance, and visuomotor adaptation; - The associations varied depending on age, task type, and learning processes (implicit and explicit); In older adults, motor performance in a sequential motor task (Grooved pegboard test) was influenced by HPA scores, with higher HPA scores linked to lower performance; - For young adults, performance on the visuomotor task was influenced by HPA scores, where higher scores were associated with faster visuomotor adaptation, especially in those naïve to the perturbation; - Although genotype associations were amplified by age in both the Grooved pegboard test and sequential learning test, the results of the visuomotor adaptation task did not support this trend.

APOE - Apolipoprotein E; ANKK1 - ankyrin repeat and kinase domain containing 1; BDNF - Brain-Derived Neurotrophic Factor; BIS - Berlin Intelligence Structure; COMT - catechol-O-methyltransferase; DKEFS - Delis-Kaplan Executive Function System Trail Making subtest; DRD2 - dopamine D2 receptor; ERP - Event-Related Potential; HPA - high-performance alleles; TMT - Trail Making Test; WAIS - Wechsler Adult Intelligence Scale; WCST - Wisconsin Card Sorting Test; WM - working memory. *The novelty-P3 (nP3) response, recorded on the scalp through electroencephalography, is associated with context updating processes in response to sensory novelty; **Not used in the analysis.

BDNF, BDNF gene, Val66Met (rs6265) polymorphism of the BDNF gene, and hippocampus

BDNF is a secretory neurotrophin belonging to the family of NTs that plays a fundamental role in neural survival, growth, modulation of synaptic transmission, neurogenesis, memory function, and synaptic plasticity. BDNF levels in peripheral tissues, brain, and blood can be influenced by the polymorphism of the BDNF gene³³. Located on chromosome 11p13, the BDNF gene consists of five or more exons, each with its own promoter region²¹. This gene encodes a precursor peptide (proBDNF), which is proteolytically cleaved to form mature BDNF (mBDNF). A relevant polymorphism related to this gene is Val66Met (rs6265), a SNP located at nucleotide 196 (G/A), which results in the substitution of valine for methionine at codon 66 of the pro-domain of BDNF. This variation affects intracellular trafficking and the regulation of BDNF secretion. Individuals with the Met/Met and Val/Met genotypes exhibit reduced neurotrophic support from BDNF for plasticity, impaired intracellular trafficking, and decreased regulated secretion of BDNF in neurons, while individuals with the Val/Val genotype demonstrate the opposite. As a result, there is reduced BDNF production in the central nervous system and lower circulating levels of this NT in individuals with Val/Met and Met/Met genotypes³⁴.

The authors highlight important considerations regarding studies that investigated BDNF and the Val66Met polymorphism²¹. In summary, these considerations are: (1) studies in animal models suggest that BDNF protects neurons

from damage, plays a crucial role in modifying synaptic connections, and modulates long-term potentiation (LTP) in the hippocampus; (2) studies in humans have shown that the Met allele is associated with reduced volume or lower functional activity of the hippocampus; (3) genetic research on the Val66Met polymorphism indicated that the Met allele is linked to poorer performance in memory tests and EFs. Based on these different sources of evidence, the authors suggest that the Val66Met polymorphism likely influences memory performance and possibly EFs, although further studies are needed to confirm the latter point²¹. The COMT and BDNF genes may interactively influence EFs³⁵. Based on this premise, two main points can be highlighted: (1) brain regions such as the PFC and the medial temporal lobe (MTL) — which includes the hippocampus — are strongly interconnected and co-activated during various tasks requiring EFs; (2) although the COMT gene is traditionally associated with the PFC and the BDNF gene with the MTL⁽³⁵⁾³⁴, both genes affect these two brain regions. Furthermore, the Val66Met polymorphism of the BDNF gene has been associated with variation in human cortical morphology. For example, individuals carrying the Met allele show reduced gray matter volume in the PFC as well as in the hippocampus³⁶ and tend to perform worse on the Wisconsin Card Sorting Test (WCST), a test used to assess PFC function³⁷. These findings suggest that BDNF plays an important role in the integrity of the PFC and in performance on tasks related to EFs.

Factors beyond gene-gene interaction in the interpretation and consistency of results

(1) Neuropsychological tests and tasks have limitations in identifying cognitive processes sensitive to genetic variation, as there is no direct linear relationship between task performance and the activation of a specific neural circuit²¹. To address this limitation, it was suggested using alternative phenotypes, such as brain activity measured by functional magnetic resonance imaging (fMRI)³⁸. fMRI allows for direct observation of which areas of the brain are activated during a cognitive task, providing a more accurate connection to the underlying neural function. Thus, instead of relying solely on the results of traditional neuropsychological tests or tasks, researchers can use brain imaging to investigate how different genetic variants influence neuronal activation.

In summary, neuropsychological tests and tasks may be insufficient to accurately identify the genetic effects on cognition, and other tools may provide a more reliable approach. In this sense, methods such as electroencephalography and eye-tracking (oculomotor behavior – sensory information that influences the decisional stage, related to cognitive processes) can also be used. The study conducted by Garcia-Garcia¹⁸ employed an electroencephalographic measure called nP3, which reflects context updating operations involved in processing sensory and task-related novelties. This measure has been

established as a brain signature of context information updating.

(2) Different neuropsychological tests and tasks have distinct characteristics, which uniquely impact the effect size and the results of studies²¹. Some examples include: using different tests or tasks to investigate the same cognitive process, employing tasks with varying levels of complexity, or using a single task to measure WM as a whole, without separating it into distinct subcomponents.

(3) The results obtained from the studies are reported inconsistently. For example, homozygous and heterozygous groups are sometimes grouped together, while at other times, they are analyzed separately.

Regarding the polymorphism of the DRD2/ANKK1 gene, two notable points for grouping A1 homozygotes and A1/A2 heterozygotes are: (a) the presence of just one A1 allele already causes a reduction in the density of dopamine D2 receptors²⁷; (b) the A1/A1 genotype is extremely rare, occurring in approximately 3% of the healthy Caucasian population³⁹ (which is more commonly investigated in studies). For this reason, it is common to group the A1/A1 genotype with the A1/A2 genotype in genetic association studies.

Regarding the polymorphism of the COMT gene, studies show that, since the alleles are codominant, Val/Met heterozygotes exhibit intermediate levels of COMT activity and DA availability^{14,15}. However, genetic association studies also group individuals based on the presence of the Val allele,

forming the Val+ group. In Stelzel's⁶ study, the authors grouped the Val/Val and Val/Met genotypes into the Val+ group. They then performed a post hoc analysis of the factor scores for the three components of WM, testing for heterosis effects. When considering the Val/Met genotype as a separate factor between subjects, a COMT · DRD2 interaction was observed only for WM manipulation ($p < 0.05$). The Val/Met group scored at an intermediate performance level in both DRD2 subgroups (A1-, A1+).

(4) Several factors modulate the dopaminergic system: age-related changes, with normal aging being associated with a general reduction in dopaminergic neuromodulation; cigarette consumption, where nicotine directly and indirectly enhances dopaminergic transmission, for example, by activating nicotinic acetylcholine receptors in dopaminergic neurons; neurological conditions (such as Parkinson's disease) and psychiatric or neurodevelopmental disorders; gender, as studies suggest that estrogens inhibit the transcription of the COMT gene, among other factors; and ethnic diversity, with linkage disequilibria of the COMT gene in allele frequencies of polymorphisms, such as Val158Met, that vary substantially across different populations⁴⁰.

CONCLUSION

The aim of this narrative review was to compile studies on polymorphisms in genes associated with the PFC, basal ganglia, and hippocampus, and explore their implications for

cognitive and motor functions. While some studies identified clear associations between certain genotypes and performance on cognitive and motor tasks, others presented inconclusive results. This suggests that the influence of these polymorphisms may be modulated by other genetic and environmental factors that are not yet fully understood. In studies investigating interactions between polymorphisms, complex interactions were identified that result in varied effects, depending on the balance between neurotransmitters and receptors in different brain regions. These interactions were particularly evident in the polymorphisms of the COMT and DRD2 genes. Additionally, considering the interaction among the three polymorphisms, the effects were more pronounced in alleles considered to have high performance in literature. Understanding these polymorphisms is essential to elucidate the functioning of brain regions and their interactions, as well as the impact of these interactions on cognitive/executive and motor functions. Cognitive/EFs, in particular, are fundamental to individuals' daily life aspects and may influence motor functions. Future investigations should consider these interactions more comprehensively, including other genetic and environmental variables, such as the type of tasks investigated and sample size, for a deeper and more accurate understanding of the underlying mechanisms of cognitive and motor functions.

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