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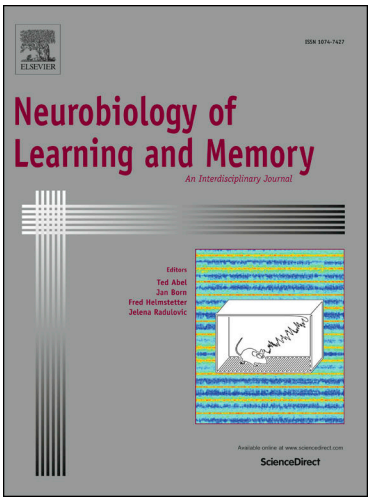

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PII: S1074-7427(20)30001-0
DOI: https://doi.org/10.1016/j.nlm.2020.107157
Reference: YNLME 107157

To appear in: *Neurobiology of Learning and Memory*

Received Date: 3 September 2019
Revised Date: 3 December 2019
Accepted Date: 3 January 2020

Please cite this article as: Gardênia de Holanda Marinho Nogueira, N., Marques de Miranda, D., Rodrigues Albuquerque, M., de Paula Ferreira, B., Túlio Silva Batista, M., Otoni Parma, J., Apolinário-Souza, T., Eduardo Antunes Bicalho, L., Ugrinowitsch, H., Menezes Lage, G., Motor learning and COMT Val158met polymorphism: analyses of oculomotor behavior and corticocortical communication, *Neurobiology of Learning and Memory* (2020), doi: https://doi.org/10.1016/j.nlm.2020.107157

Motor learning and COMT Val158met polymorphism: analyses of oculomotor behavior and corticocortical communication

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Abstract

Differences in motor learning can be partially explained by differences in genotype. The catechol-O-methyltransferase (COMT) Val158Met polymorphism regulates the dopamine (DA) availability in the prefrontal cortex modulating motor learning and performance. Given the differences in tonic and phasic DA transmission, this study aimed to investigate whether the greater cognitive flexibility associated with the Val allele would favor the learning of movement parametrization, while the greater cognitive stability associated with the Met allele favors the acquisition of the movement pattern. Furthermore, we investigated if the genotypic characteristics impact visual

scanning of information related to parametrization and to the movement pattern, and the level of cortical connectivity associated with motor planning and control. Performance and learning of a sequential motor task were compared among three genotypes (Val/Val, Val/Met, and Met/Met), as well as their oculomotor behavior and level of cortical coherence. The findings show that the cognitive flexibility promoted by the Val allele is associated with a better parametrization. The search for information through visual scanning was specific to each genotype. Also, a greater cortical connectivity associated with the Val allele was found. The combined study of behavioral, electrophysiological and molecular levels of analysis showed that the cognitive stability and flexibility associated with the COMT alleles, influence specific aspects of motor learning.

Keywords: Motor behavior. COMT polymorphism. Genetics. EEG. Vision.

1 Introduction

Motor stability and flexibility are two important features involved in the acquisition of skilled behavior (Glencross, Whiting & Abernethy, 1994). Motor stability refers to the production of a well-defined spatio-temporal pattern over time. Motor flexibility, on the other side, refers to the ability of adjusting this spatio-temporal pattern to the environmental demands, maintaining its identity (Apolinário-Souza et al., 2016). Learning the skill's relative (or invariant) dimension, which is characterized by the ability to reproduce a well-defined temporal pattern of the movement's components (Schmidt, 2003), is associated with increased stability. Conversely, learning the skill's absolute (or variant) dimension, characterized by the total time parametrization ability (Shea & Wulf, 2005), is associated with increased flexibility in behavior (Apolinário-Souza et al., 2016; Lai, Shea, Wulf & Wright, 2000; Lai & Shea, 1998). Sequential motor tasks, with both a relative and an absolute timing goal, can be used to assess improvements in stability and flexibility throughout practice (Apolinário-Souza et al., 2016; Lage et al., 2007; Lai et al., 2000; Lai & Shea, 1998).

Individual differences can influence improvements in stability and flexibility, which reflect the acquisition of a motor skill. For instance, genes with cerebral effects influence an individual's behavior (Meyer-Lindenberg et al., 2006), such as the COMT gene (Diamond, Briand, Fossella & Gehlbach, 2004). COMT has genetic variants that influences dopaminergic transmission and is involved in motor and cognitive performances related to the prefrontal cortex (PFC) and to dopamine (DA). Dopamine levels in the PFC are affected by the catechol-o-methyltransferase (COMT) enzyme availability (Baetu, Burns, Urry, Barbante & Pitcher, 2015; Krause, Beck, Agethen & Blischke, 2014; Lage et al., 2014).

A trimodal distribution of the COMT activity is found in human populations due to a functional polymorphism called Val158Met (rs4680). Its coding sequence consists of a G → A trade off, which results in a valine (Val) replaced by a methionine (Met) at position 158 of the MB-COMT (108 of S-COMT) (Tunbridge, Harrison & Weinberger, 2006). The Met homozygotes have lower thermostability, presenting lower activity in physiological temperature (Chen et al., 2004). Its degradation rate is 1/3 to 1/4 slower, resulting in more DA available within synaptic clefts. Conversely, the Val homozygotes show greater enzyme activity and lower DA concentration in synaptic clefts (Tunbridge et al., 2006). Given the codominance of the alleles, the Val/Met heterozygotes have

intermediate levels of the COMT activity (Egan et al., 2001; Tunbridge et al, 2006; Wahlstrom et al., 2007).

Functional effects of the COMT polymorphism in DA neurotransmission can be better understood by emergent ideas regarding the roles played by tonic and phasic DA in cognitive processing (Bilder, Volavka, Lachman & Grace, 2004; Grace, 1991). Tonic stimulation of the cortical D1 receptors stabilizes and maintain relevant information, while phasic stimulation of the striatal D2 receptors provides cognitive flexibility, updating and manipulating information (Grace, 1991; Rosa, Dickinson, Apud, Weinberger & Elvevag, 2010). Therefore, it was suggested that the Met allele is associated with an increased tonic DA activity, resulting in cognitive stability, while the Val allele is associated with increased phasic DA activity, resulting in cognitive flexibility (Bilder et al., 2004; Rosa et al., 2010).

Studies of cognitive functions and studies of motor behavior indicate differences in learning and performance between Val and Met homozygotes of the COMT polymorphism (Baetu et al., 2015; Krause et al., 2014; Malloy-Diniz et al., 2013; Nolan, Bilder, Lachman & Volavka, 2004; Noohi et al., 2014, 2016; Rosa et al., 2010; Witte et al., 2012). Moreover, there are evidences of distinct effects of the COMT genotypes in the roles played by tonic and phasic DA. However, within the motor domain there is a need for research investigating the specific effects of DA activity on flexibility and stability. For example, if these effects are more related to acute (motor control and acquisition) or long-term effects (learning). The studies relating the COMT Val158Met polymorphism and motor learning did not investigate this association in a sequential motor task demanding simultaneous improvement of stability and flexibility (Nogueira, Bacelar, Ferreira, Parma & Lage, 2019). Our hypothesis is that the cognitive stability associated with the Met allele favors the production of a spatio-temporal pattern throughout the acquisition of a sequential motor task, while the updating and manipulation of information related to the Val allele favors the ability to adjust the spatio-temporal pattern to the dynamics of the environment.

Investigating the mechanisms underlying the relation between motor learning and genotype is also necessary. Searching for information in the environment to feed perceptive processes is crucial to motor planning and control (Bicalho et al., 2019; Lelis-Torres, Ugrinowitsch, Apolinário-Souza, Benda & Lage, 2017). Throughout learning of a sequential motor task, the learner deals with information of (a) the spatio-temporal goal, or movement pattern to be executed, and (b) parametrization, or small trial-to-trial adjustments in the movement pattern (Lage et al., 2017). Learners carrying the Met allele may predominantly search for information about goal and feedback related to the stable dimension to be learned, referring to the movement pattern. The Val allele carriers may predominantly search for information related to the flexibility demands, referring to movement parametrization. Analysis of oculomotor behavior can test the hypothesis that the cognitive characteristics of stability and flexibility caused by the COMT alleles are associated with the type of information that feeds the initial stages of motor planning and control.

Another mechanism of interest in this study is corticocortical communication. It refers to the communication between cortical areas during task execution (Brauns et al., 2014) and can be observed throughout practice through refinement of the communication between cortical areas (Gentilli et al., 2015). Changes in the movement representation

resulting from participation of different cerebral structures are dependent not only on the learning phase, but also on the features of the task (Dayan & Cohen, 2011; Doyon, Penhune & Ungerleider, 2003). In the initial phase of learning of sequential motor tasks, the cortico-striatal and cortico-cerebellar circuits are jointly activated. The prefrontal areas, motor areas, striatum and the cerebellum are associated with the encoding of motor sequence programs. As practice continues and an asymptotic performance is progressively reached, the role of the cortico-striatal circuit is increased, while the role of the cortico-cerebellar is decreased (Doyon, Gabitov, Vahdat, Lungu & Boutin, 2018). Differences in prefrontal DA activity produced by the COMT genotypes can change the functionality of the cortico-striatal circuit. If cognitive stability associated with the Met allele favors the production of the movement pattern and cognitive flexibility associated with the Val allele favors parametrization, different levels of corticocortical communication throughout practice can be expected between Met and Val alleles carriers. Therefore, this study aims to investigate the association between the COMT Val158Met polymorphism and the acquisition of a sequential motor task. The hypotheses are that (a) the Met allele will favor the production of the movement pattern and the Val allele will favor the movement parametrization; (b) Met allele carriers will predominantly search for information related to the movement pattern and the Val allele carriers will predominantly search for visual information related to parametrization; (c) the levels of corticocortical communication will be different between Met and Val alleles carriers.

2 Methods

2.1 Participants

This study included a final sample of 42 right-handed undergraduate students, mean (M) age of 25.12 years (standard deviation [SD] = 5.84), with 15 women (M_{age} = 24.20, SD = 6.09 years) and 27 men (M_{age} = 25.63, SD = 5.76 years). We selected this group as a subset of our initial sample of 100 participants in a procedure to be described later. All participants had normal or corrected-to-normal vision, declared no history of neurologic or psychiatric impairment or medication use that could alter brain functions, and scored at least 80 points on the Edinburgh Handedness Inventory (Oldfield, 1971), indicating right hand preference. All participants signed written informed consent after receiving a full explanation of the study. An ethics committee from a local university approved all procedures, and we conformed to the standards set by the Declaration of Helsinki (2014 version).

2.2 Genotyping

We used the high salt method to extract the DNA of participants from a blood sample. We diluted DNA samples in Tris-EDTA pH 8.0 and stored them at 4 ºC. We amplified DNA material by real time polymerase chain reaction (PCR), and we analyzed the COMT functional polymorphism (Val158Met rs4680) with the TaqMan Genotype assay (Applied Biosystems, CA). We followed the fabricant marker instructions to perform PCR, which contained: 3.5 ul TaqMan Genotyping Master Mix, 3.4 ul deionized water, 0.1 ul TaqMan Genotype Assay (Applied Biosystems, Foster City, CA), and 1.0 ul of DNA with final concentration of 50 ng/ul. The PCR parameters included an initial denaturation at 95 ºC for 10 minutes, followed by 50 cycles at 95 ºC for 15 seconds, and 60 ºC for one minute. We determined genotype based on the allelic discrimination mode

(CFX Manager Software; Bio-Rad Laboratories, Hercules, CA; version 3.1, 2012). Personnel involved in genotyping were blind to neuropsychological results, and we used 10% of the genotypes for quality control. We conducted genotyping of our initial sample of 100 participants. From these, only 14 participants were found with the Met/Met COMT polymorphism. We then comprised equal sized groups of Val/Met and Val/Val participants to balance the size of our groups, also matching the number of females and males in the Met/Met group with the Val/Val and Val/Met groups. We randomly assigned the female and male participants from the Val/Val and Val/Met groups.

2.3 Apparatus

To conduct the experimental task, a 49 inches 4K/Ultra HD-LED television (LG, Seoul, South Korea) and a numeric keypad were placed on a standard table and connected to a microcomputer (Dell, Texas, EUA, XPS 8920). We used a specific software to control the experimental task and to register the time in-between key pressings (see below for a description of the motor task). We used an electroencephalographic and an oculometry (eye-tracker) system. The eye-tracker system consisted of a SensoMotoric mobile eye tracker connected to a laptop computer (SMI, Berlin, Germany). The eye-tracking data was recorded at 30 Hz using the SMI iViewX2.7 software system (SMI, Berlin, Germany). We used the Emotiv Epoc+ (Emotiv Technology Inc., San Francisco, EUA) EEG system. The EmotivPRO system (Emotiv Technology Inc., San Francisco, EUA) was used to acquire and record the raw data of the electroencephalography. We used sixteen electrodes to acquire the electrical activity from the participants' scalp: AF3, F7, F3, FC5, T7, P7, O1, O2, P8, T8, FC6, F4, F8, FC4, M1 e M2. The positioning of these electrodes followed the international 10-20 system (Jasper, 1958). The electrodes on both mastoid process (M1 and M2) were used as reference electrodes. The EEG sample rate was 128 Hz to all channels.

2.4 Sequential motor task

Participants were asked to sequentially press four keys (2, 8, 6, and 4) on the numeric keypad, using the index finger of the right hand. The total criteria movement times were 700, 900, or 1,100 ms, and the relative criteria segment ratios were 22.2% (key 2-8), 44.4% (key 8-6), and 33.3% (key 6-4) (Figure 1B). Each participant randomly executed 40 trials of each total criterion movement time, with no consecutive repetition of a same criterion. Contrary to the continuous variation of the total criterion time, the relative segment ratios did not vary throughout practice, demanding the learning of only one movement pattern. After finishing the sequence (pressing key 4), the knowledge of results (KR) was presented for a minimum of 6 seconds. Quantitative KR consisted of (1) the ratio performed for each segment (22.2%, 44.4%, and 33.3%), (2) total relative error (sum of the differences between the criterion segment ratio and the ratio performed for each segment), and (3) the total time performed by the participant, in milliseconds. After six seconds, the "start" sign appeared on the screen together with the presentation of the new total criterion time, so participants could start the next trial whenever they wanted. Information regarding the relative segment ratios also appeared at each new trial, despite being unaltered. KR was available on the screen until the pressing of the key 2.

We considered pieces of information related to cognitive stability: (a) the relative criteria segment ratios before execution, (b) KR of the ratio performed for each segment, and (c) total relative error. Information related to cognitive flexibility were: (a) total criterion movement time before execution, and (b) KR of the total time performed.

2.5 Procedures

In the first day, participants signed the written informed consent and we provided them detailed instructions about the task and procedures. They completed the Edinburgh Handedness Inventory (Oldfield, 1971). We also extracted the participants' blood sample to posterior genotyping. After the genotyping process of all participants' DNA, participants of our three groups (Val/Val, Met/Met, and Val/Met) were defined as described earlier, and we contacted the participants who constituted our final sample. The motor task was performed in two consecutive days. The acquisition phase was performed in the first day, and the learning tests 1 and 2 were performed after approximately 24 h from the end of acquisition. The learning test 1 was performed with the total timing criterion of 900 ms. Immediately after, the learning test 2 was performed with the total timing criterion on 1,300 ms. Both learning tests consisted of 12 trials each, with the same relative criteria segment ratios as practiced during the acquisition phase. The learning test 1 demanded the production of an already practiced parameter (900 ms) in a novel context, since it was performed with a constant scheduling, without the variations of the acquisition phase. The learning test 2 demanded the production of an unpracticed parameter (1,300 ms) also in a novel context (constant practice).

The electroencephalography and oculometry devices were positioned on participants after they were comfortably seated, before the acquisition phase and learning test 1.

2.6 Eye-tracker signal processing

The eye-tracker data was evaluated through a custom-made routine on Matlab (The Mathworks Inc., Massachusetts, EUA). The recorded eye-tracker "world camera" of each participant was extracted to identify the position of each KR and task goals, thus we identified the type and amount of information that feeds the initial stages of motor planning and control. The first image frame of the video was extracted to provide a reference and comparison image with the world camera video to compute each KR/task goals (Figure 1D). Areas of interests (AOI) vectors of each KR and task goals displayed on the screen were then built using artificial system techniques which are detailed elsewhere (Bicalho et al., 2019). The analysis of gaze was further analyzed by a processing technique that involved the extraction of its RGB values and the metrics of its connected components.

2.7 EEG signal processing

The EEG device was used during the entire acquisition phase and learning tests. We used the Phase Locked Value (Lachaux, Rodriguez, Martinerie & Varela, 1999) technic of temporal series analysis. When two cortical areas are synchronized, the coherence (Coh) between them increases, consequently strengthening the communication between these areas (Fell & Axmacher, 2011).

We used the following electrodes combination: F3F4, F4P8, F4FC6, F3P7, and F3FC5. The cortical regions of interest were: secondary motor areas, prefrontal areas, and parietal areas, represented by the electrodes F4F3 and FC6FC5, functionally responsible by motor planning, volitional action control, and executive functions, and P7P8, due to their relationship with sensorimotor integration. The Coh values were calculated in 10 blocks of 12 trials to the acquisition phase, and 1 block of 12 trials to each learning test for the targeted Theta band (4-7 Hz), which is associated with cognitive processing, mainly controlling working memory processes (Brauns et al., 2014; Sauseng, Griesmayr, Freunberger & Klimesch, 2010), with the identification and coding of sensorial stimuli, and with mechanisms of sensorimotor integration (Brauns et al., 2014).

We acquired EEG data through the EmotivPRO, a software provided by the own EEG manufacturer. Data from the motor task and EEG were synchronized offline by an algorithm developed in MATLAB (Natick, MA, EUA) to this specific end (Figure 1C). The program that controlled the motor task registered timestamps of: (1) begin of EEG recording, (2) each moment in which key 2 was pressed and (3) each moment in which key 4 was pressed. Thus, we defined both the planning (the intervals between pressing key 4 and key 2), and the execution phases (the intervals between pressing key 2 and pressing key 4). The same computer in which the timestamps were recorded was used for EEG recording.

[Insert Figure 1 about here – 2 column fitting image]

2.8 Measurements

Two dependent motor variables were measured: (1) the absolute error (AE) and (2) the relative error (RE). The AE provides information about cognitive flexibility during acquisition and learning tests, while the RE provides information about stability. The AE was computed as the difference between the performed movement time and the total criterion time:

$$AE = (MTn - \text{total criterion time}).$$

The RE was determined as the sum of absolute differences between the observed and criterion time ratio for each segment computed as follows (Apolinário-Souza et al., 2016; Lelis-Torres et al., 2017):

$$RE = |R1 - 22.2| + |R2 - 44.4| + |R3 - 33.3| \times 100.$$

where Rn = (the actual movement time of segment/total movement time) × 100.
To measure the amount of visual information gathered on KR and goals during the acquisition phase, the total dwell time (TDT) on each AOI was computed to both relative and absolute dimensions. TDT was defined as the total amount of time a participant fixates in an AOI related to KR or goals information. The TDT was normalized into seconds, partitioned into trials/blocks and further segmented into feedback period (FP) and planning period (PP). The FP comprises the 6 s period of visual search that occurs between the last key pressing and the appearance of the message “Start” while the PP encompasses the meantime between the appearance of the

message and the pressing of the first key of the next trial sequence. During the PP, feedback information was also available.

We used the Coh by Phase Locked Value as the electroencephalographic measure (Lachaux et al., 1999). Coh varies from 0 (absence of phase synchronization) to 1 (perfect phase synchronization) indicating the level of corticocortical communication between two electrodes.

2.9 Statistical analyses

The Shapiro-Wilk test revealed that all measures had a normal distribution. Thus, data were organized as means and standard deviations for descriptive analyses. The measures of motor performance were organized in blocks of 12 trials. The AE and RE on the acquisition phase were analyzed using a two-way ANOVA (3 Groups × 10 Blocks) with repeated measures on the second factor. We conducted one-way ANOVAs (3 Groups × 1 Block) to analyze the learning tests 1 and 2.

To investigate the changes in the amount of visual information gathered on KR and task goals from the first to the last block of acquisition, the TDT was analyzed using two-way ANOVAs (3 Groups × 2 Blocks) with repeated measures on the last factor. Thus, we conducted 8 analyses: (1) TDT on relative timing goal: planning period; (2) TDT on relative timing goal: feedback period; (3) TDT on absolute timing goal: planning period; (4) TDT on absolute timing goal: feedback period; (5) TDT on relative timing KR: planning period; (6) TDT on relative timing KR: feedback period; (7) TDT on absolute timing KR: planning period; (8) TDT on absolute timing KR: feedback period.

Regarding the analysis of Coh, we used a two-way ANOVA (3 Groups × 5 Pairs of Electrodes) with repeated measures on the last factor on the acquisition phase and on each learning test. These analyses were performed to each moment (planning and execution) for the targeted band.

We used Tukey's test for post hoc analyses. We set the level of statistical significance at 0.05 for all statistical tests. The effect sizes were calculated using partial eta-squared (ηp2).

3 Results

3.1 Absolute dimension analyses

Flexibility-related motor performance - Absolute error (AE)

Acquisition phase

We present descriptive analyses in Figure 2. The inferential analysis detected a significant main effect for Groups [$F_{(2,39)} = 3.81$, $p = .03$, $\eta p2 = 0.16$]. Post hoc analysis indicated that the Val/Val group was superior to the Met/Met group ($p = .04$, $d = 1.84$). The inferential analysis also detected a significant main effect for Blocks [$F_{(1,9)} = 14.65$, $p < .01$, $\eta p2 = 0.27$]. First block errors were significantly greater compared with the other blocks ($p < .01$). A significant interaction between Groups and Blocks [$F_{(2,18)} = 2.63$, $p = .03$, $\eta p2 = 0.12$]. Post hoc analysis indicated that the Met/Met group was inferior to the Val/Val group on blocks 2 ($p = .02$, $d = 1.05$), 3 ($p = .03$, $d = 1.00$), 4 ($p =$

.001, d = 1.28) and 9 (p = .01, d = 1.26), and inferior to the Val/Met group on block 2 (p = .03, d = 0.88). The Val/Met group was inferior to the Val/Val group on blocks 4 (p < .01, d = 1.51), 9 (p < .01, d = 1.03) and 10 (p = .02, d = 1.18). All groups performed better on the last block than on the first block of acquisition, Val/Val (p = .001, d = 2.21), Val/Met (p < .001, d = 1.34), and Met/Met (p = .001, d = 1.86).

Learning tests

Descriptive statistics are presented in Figure 2. The inferential analysis detected a significant difference for groups on learning test 1 [$F_{(2,39)}$ = 3.324, p = .05, ηp2 = 0.17]. Post hoc analysis indicated that the Val/Val group was superior to the Met/Met group (p = .04, d = 0.86). No significant difference was found for groups on learning test 2 [$F_{(2,39)}$ = 2.06, p = .14, ηp2 = 0.10].

3.2 Relative dimension analyses

Stability-related motor performance - Relative error (RE)

Acquisition phase

Descriptive statistics are presented in Figure 2. The inferential analysis did not detect a significant main effect for Groups [$F_{(2,39)}$ = 0.21 p = .81, ηp2 = 0.01], but indicated a significant main effect for Blocks [$F_{(1,9)}$ = 10.10, p < .01, ηp2 = 0.75]. Post hoc analysis indicated that first block errors were significantly larger compared with errors in other blocks (p < .01). No significant interaction between Groups and Blocks was found [$F_{(2,18)}$ = 1.36, p = .21, ηp2 = 0.07].

Learning tests

Descriptive statistics are presented in Figure 2. The inferential analysis did not detect a significant main effect for Groups on learning test 1 [$F_{(2,39)}$ = 0.29, p = .75, ηp2 = 0.01], or learning test 2 [$F_{(2,39)}$ = 0.22, p = .81, ηp2 = 0.01].

[Insert Figure 2 about here – 2 column fitting image]

3.3 Total dwell time

Total dwell time on absolute timing KR: Planning period

Descriptive statistics are presented in Figure 3. The inferential analysis on TDT indicated a significant main effect for Groups [F(2,39) = 3.55, p = .04, ηp2 = 0.15]. The post hoc analysis indicated that the Val/Val group presented higher TDT than the Met/Met group (p = .03, d = 0.57). The inferential analysis detected a significant main effect for Blocks [F(1,39) = 33.28, p < .01, ηp2 = 0.46]. The post hoc analysis indicated that TDT decreased from first to the last block of trials (p < .001, d = 1.31). There was no significant interaction between Groups and Blocks [F(2,78) = 0.60, p = .55, ηp2 = 0.03].

Total dwell time on absolute timing KR: Feedback period

Descriptive statistics are presented in Figure 3. The inferential analysis on TDT indicated a significant main effect for Groups [$F(2,39) = 3.24$, $p = .05$, $\eta p2 = 0.14$]. The post hoc analysis indicated that the Val/Val group presented a higher TDT than the Val/Met ($p = .04$, $d = 0.33$) group. The inferential analysis detected a significant main effect for Blocks [$F(1,39) = 99.16$, $p < .01$, $\eta p2 = 0.72$]. The post hoc analysis indicated that TDT decreased from the first to the last block of trials ($p < .001$, $d = 2.50$). There was no significant interaction between Groups and Blocks [$F(2,78) = 0.29$, $p = .75$, $\eta p2 = 0.02$].

Total dwell time on relative timing KR: Planning period

Descriptive statistics are presented in Figure 3. The inferential analysis on TDT did not detect a main effect for Groups [$F(2,39) = 1.11$, $p = .34$, $\eta p2 = 0.05$], but detected a significant main effect for Blocks [$F(1,39) = 111.53$, $p < .01$, $\eta p2 = 0.74$]. The post hoc analysis indicated that TDT decreased from the first to the last block of trials ($p < .001$, $d = 1.73$). There was no significant interaction between Groups and Blocks [$F(2,78) = 0.50$, $p = .61$, $\eta p2 = 0.03$].

Total dwell time on relative timing KR: Feedback period

Descriptive statistics are presented in Figure 3. The inferential analysis on TDT indicated a significant main effect for Groups [$F(2,39) = 3.77$, $p = .03$, $\eta p2 = 0.16$]. The post hoc analysis indicated that the Met/Met group presented a higher TDT than the Val/Val group ($p = .03$, $d = 0.58$). The inferential analysis detected a significant main effect for Blocks [$F(1,39) = 27.45$, $p < .01$, $\eta p2 = 0.41$]. The post hoc analysis indicated that TDT decreased from the first to the last block of trials ($p < .001$, $d = 1.16$). There was no significant interaction between Groups and Blocks [$F(2,78) = 1.37$, $p = .27$, $\eta p2 = 0.07$].

Total dwell time on absolute timing goal: Planning period

Descriptive statistics are presented in Figure 3. The inferential analysis on TDT indicated a significant main effect for Groups [$F(2,39) = 38.78$, $p < .01$, $\eta p2 = 0.67$]. The post hoc analysis indicated that the Val/Val group presented a higher TDT than the Met/Met ($p < .001$, $d = 1.74$) and Val/Met ($p < .001$, $d = 1.14$) groups. The inferential analysis detected a significant main effect for Blocks [$F(1,39) = 152.03$, $p < .01$, $\eta p2 = 0.80$]. The post hoc analysis indicated that TDT decreased from the first to the last block of trials ($p < .001$, $d = 1.48$). There was no significant interaction between Groups and Blocks [$F(2,78) = 0.86$, $p = .43$, $\eta p2 = 0.04$].

Total dwell time on absolute timing goal: Feedback period

Descriptive statistics are presented in Figure 3. The inferential analysis on TDT indicated a significant main effect for Groups [$F(2,39) = 15.83$, $p < .01$, $\eta p2 = 0.45$]. The post hoc analysis indicated that the Val/Val group presented a higher TDT than the Met/Met ($p < .01$, $d = 0.15$) and Val/Met ($p < .001$, $d = 0.25$) groups. The inferential analysis detected a significant main effect for Blocks [$F(1,39) = 3448.51$, $p < .01$, $\eta p2 = 0.99$]. The post hoc analysis indicated that TDT decreased from the first to the last block of trials ($p < .001$, $d = 9.51$). A significant interaction between Groups and Blocks was

found [F (2,78) = 10.67, p < .01, ηp2 = 0.35], and post hoc analysis indicated that the Val/Val group presented higher TDT than the Met/Met (p < .01, d = 1.52) and Val/Met (p < .001, d = 1.83) groups on the first block, and the Met/Met group presented higher TDT than the Val/Met group (p = .02, d = 0.95) on the first block.

Total dwell time on relative timing goal: Planning period

Descriptive statistics are presented in Figure 3. The inferential analysis on TDT indicated a significant main effect for Groups [F(2,39) = 26.90, p < .01, ηp2 = 0.58]. The post hoc analysis indicated that the Met/Met group presented a higher TDT than the Val/Val (p < .001, d = 0.43) and Val/Met (p < .001, d = 0.62) groups. The inferential analysis detected a significant main effect for Blocks [F(1,39) = 1316.11, p < .01, ηp2=0.97]. The post hoc analysis indicated that TDT decreased from the first to the last block of trials (p < .001, d = 6.29). No significant interaction between Groups and Blocks was found [F(2,78) = 0.11, p = .89, ηp2 = 0.01].

Total dwell time on relative timing goal: Feedback period

Descriptive statistics are presented in Figure 3. The inferential analysis on TDT indicated a significant main effect for Groups [F(2,39) = 37.90, p < .01, ηp2 = 0.66]. The post hoc analysis indicated that the Met/Met group presented a higher TDT than the Val/Val (p < .001, d = 0.40) and Val/Met (p < .001, d = 0.47) groups. The inferential analysis detected a significant main effect for Blocks [F(1,39) = 1237.67, p < .01, ηp2 = 0.97]. The post hoc analysis indicated that TDT decreased from the first to the last block of trials (p < .001, d = 4.57). A significant interaction between Groups and Blocks was found [F(2,78) = 17.14, p < .01, ηp2 = 0.47], and post hoc analysis indicated that the Met/Met group presented higher TDT than the Val/Val (p < .001, d = 1.99) and Val/Met (p < .001, d = 2.73) groups on the first block, and presented higher TDT than Val/Met group (p = .01, d = 2.55) on the last block.

[Insert Figure 3 about here – 2 column fitting image]

3.4 Corticocortical communication: Theta Band (4-7 Hz)

Planning

Acquisition phase

Descriptive statistics are presented in Figure 4. The inferential analysis detected a significant main effect for Groups [$F_{(2,39)}$ = 0.43, p = .04, ηp2 = 0.15]. Post hoc analysis indicated that the Val/Val group had greater Coh than the Val/Met (p = .03, d = 0.32) and Met/Met (p = .03, d = 0.32) groups. The inferential analysis did not detect a significant main effect for Pair of Electrodes [$F_{(1,4)}$ = 1.05, p = .38, ηp2 = 0.03] or an interaction between Groups and Pair of Electrodes [$F_{(2,8)}$ = 1.23, p = .30, ηp2 = 0.06].

Learning test 1

Descriptive statistics are presented in Figure 4. The inferential analysis detected a significant main effect for Groups [$F_{(2,39)}$ = 4.75, p = .01, ηp2 = 0.20]. Post hoc analysis

indicated that the Val/Val group had greater Coh than the Val/Met (p = .01, d = 3.33) and Met/Met (p = .01, d = 3.33) group. Also, a significant main effect for Pair of Electrodes was found [$F_{(1,4)}$ = 58.77, p < .01, ηp2 = 0.60]. Post hoc analysis indicated that the F4F3 combination had greater Coh than the F4P8 (d = 11.77), F3P7 (d = 15.30), and F3FC5 (d = 4.71) combinations, while the F4P8 combination had greater Coh than the F3P7 (d = 3.00) combination and lower Coh than the F4FC6 (d = 11.37) and F3FC5 (d = 6.00) combinations. The F4FC6 combination had greater Coh than the F3P7 (d = 14.90) and F3FC5 (d = 4.31) combinations, and the F3P7 combination had lower Coh than the F3FC5 (d = 9.00) combination (p < .05). No significant interaction between Groups and Pair of Electrodes was found [$F_{(2,8)}$ = 0.69, p = .71, ηp2 = 0.03].

Learning test 2

Descriptive statistics are presented in Figure 4. The inferential analysis detected a significant main effect for Groups [$F_{(2,39)}$ = 13.00, p < .01, ηp2 = 0.40]. Post hoc analysis indicated that the Val/Val group had greater Coh than the Val/Met (d = 0.68) and Met/Met (d = 0.54) groups (p < .01). A significant main effect for Pair of Electrodes was also found [$F_{(1,4)}$ = 64.68, p < .01, ηp2 = 0.62], and post hoc analysis indicated that the F4F3 combination had greater Coh than the combinations F4P8 (d = 10.59), F4FC6 (d = 1.33), F3P7 (d = 14.33), and F3FC5 (d = 3.00). The F4P8 combination had greater Coh than the F3P7 (d = 6.28), and lower Coh than the F4FC6 (d = 9.02) and F3FC5 (d = 7.06) combinations, while the F3P7 combination had greater Coh than the combinations F4FC6 (d = 13.00) and F3FC5 (d = 11.33) (p < .05). A significant interaction between Groups and Pair of Electrodes was found [$F_{(2,8)}$ = 2.54, p = .01, ηp2 = 0.12], and post hoc analysis indicated that the Val/Val group had greater Coh than the Val/Met and Met/Met group in the combinations F4P8 (p = .001, d = 9.5 / d = 7.25), F4FC6 (p = .01, d = 4.20 / d = 3.80), and F3P7 (p = .02, d = 4.00 / 4.00).

Execution

Acquisition phase

Descriptive statistics are presented in Figure 4. The inferential analysis did not detect a significant main effect for Groups [$F_{(2,39)}$ = 1.37, p = .27, ηp2 = 0.07], Pair of Electrodes [$F_{(1,4)}$ = 0.27, p = .87, ηp2 = 0.07], or an interaction between Groups and Pair of Electrodes [$F_{(2,8)}$ = 1.90, p = .06, ηp2 = 0.09].

Learning test 1

Descriptive statistics are presented in Figure 4. The inferential analysis detected a significant main effect for Groups [$F_{(2,39)}$ = 3.15, p = .05, ηp2 = 0.14], and post hoc analysis indicated that the Val/Val group had greater Coh than the Met/Met (p = .02, d = 3.33) group. A significant main effect for Pair of Electrodes was found [$F_{(1,4)}$ = 37.76, p < .01, ηp2 = 0.49], and post hoc analysis indicated that the F4F3 combination had greater Coh than the combinations F4P8 (d = 5.94), F3P7 (d = 12.67), and F3FC (d = 4.00), and lower Coh than the F4FC6 (d = 0.67) combination. The F4P8 combination had greater Coh than the F3P7 (d = 4.81) combination, and lower Coh than the F3FC5 (d = 2.55) combination. The F4FC6 combination had greater Coh than the combinations F4P8 (d = 6.51), F3P7 (d = 13.33), and F3FC5 (d = 4.67), while the F3FC5 combination had greater Coh than the F3P7 (d = 8.67) combination (p < .05). No significant

interaction between Groups and Pairs of Electrodes was found [$F_{(2,8)} = 1.65$, $p = .12$, $\eta p2 = 0.08$].

Learning test 2

Descriptive statistics are presented in Figure 4. The inferential analysis detected a significant main effect for Groups [$F_{(2,39)} = 4.19$, $p = .02$, $\eta p2 = 0.18$], and post hoc analysis indicated that the Val/Val group had greater Coh than the Val/Met ($p = .01$, $d = 0.32$) and Met/Met ($p = .03$, $d = 0.38$) groups. The inferential analysis detected a significant main effect for Pair of Electrodes [$F_{(1,4)} = 29.21$, $p < .01$, $\eta p2 = 0.43$]. Post hoc analysis indicated that the F4F3 combination had greater Coh than the F4P8 ($d = 7.64$), F3P7 ($d = 12.33$), and F3FC5 ($d = 3.39$) combinations. The F4P8 combination had greater Coh than the F3P7 ($d = 2.83$) combination and lower Coh than the F4FC6 ($d = 5.00$) and F3FC5 ($d = 3.75$) combinations, while the combinations F4FC6 ($d = 8.49$) and F3FC5 ($d = 7.07$) had greater Coh than the F3P7 combination ($p < .05$). No interaction between Groups and Pair of Electrodes was found [$F_{(2,8)} = 0.77$, $p = .63$, $\eta p2 = 0.04$].

[Insert Figure 4 about here – 2 column fitting image]

4 Discussion

This study investigated the association between the COMT Val158Met polymorphism and learning of a sequential motor task. Most of our hypotheses were confirmed. The Val allele favored movement parametrization. In addition, Val allele carriers predominantly searched for information related to parametrization, while Met allele carriers predominantly searched for information related to the movement pattern. The levels of corticocortical communication were different between the Val allele and the Met allele carriers. The hypothesis that the Met allele would favor learning of the movement pattern was the only which was not confirmed by our results. This study provides solutions to methodologic issues unresolved in the literature, and our findings answer unsolved questions. Such as mentioned by Nogueira et al. (2019), studies should investigate the effects of the Val and Met alleles in a single task that demands the learning of both a stable and a flexible dimension. Furthermore, more than the transient effects in practice, the long-lasting effects should be assessed through learning tests. Finally, aiming to make the demand of cognitive flexibility challenging enough, it is suggested that variations of the task are presented randomly. Our results indicate that our methodological approach was adequate to assess differences between the Val and Met alleles in learning and in its underlying mechanisms.

The best performance of the Val/Val group in the acquisition phase and learning test 1 may be explained by their increased phasic dopamine transmission, which favors cognitive flexibility (Bilder et al., 2004; Rosa et al., 2010). This capacity is required by the absolute dimension of the task, which demands trial-to-trial updating and manipulation of information. This greater cognitive flexibility is possibly associated with many factors such as increased level of phasic DA, stimulation of the D2 receptors, diminished subcortical tonic DA release, diminished global DA concentration in the PFC, and diminished stimulation of the cortical D1 receptors (Bilder et al., 2004). Most of the studies that investigated the effects of the COMT polymorphism in sequential

motor tasks (Baetu et al., 2015; Noohi et al., 2014, 2016; Witte et al., 2012) did not analyze the long-lasting effects of practice, with the exception of Krause et al. (2014), which used a retention test 24 h after practice. Our study is the first to show that the beneficial effects of the Val allele in updating and manipulation of information were long-lasting. For the first time, these effects were observed in a learning transfer context.

The Val/Val group performed better than the Met/Met group on a learning test that required a different type of information processing. The learning test 1 required the retrieval and consecutive performance of only one of the parameters values previously practiced on acquisition. According to the hypothesis of transfer-appropriate processing (Bransford, Franks, Morris & Stein, 1979), performing the skill in a constant way on learning tests after having practiced it randomly on acquisition does not favor an appropriate transfer from the practice to the test context. A better transfer occurs when the processing experienced during practice is similar to the one required on the transfer test. Neural activation observed on transfer is associated with the brain activation verified in later stages of acquisition (Seidler, 2010; Seidler & Noll, 2008). If the transfer requirements are different from that processed in the final part of acquisition, this overlap of brain processes cannot occur effectively (Lage et al., 2017). The challenge presented on learning test 1 demanded cognitive flexibility, which was better observed in the Val/Val group than in the Met/Met group. The Val/Met group showed intermediate performance. A similar result regarding the Val/Met heterozygotes was found in a study using a sequential motor task (Krause et al., 2014). The processes of updating and manipulating three different parameters during acquisition were better experienced by the Val alleles carriers, which reflected in better performance and, presumably, in a stronger memory representation. Assuming the transfer-appropriate processing hypothesis, the Val/Val group should have suffered more when the retrieval and maintenance of only one parameter was required in the learning test. However, since the Val allele carries presented an inherent increased cognitive flexibility, they quickly adapted their well-learned experiences to a new processing context. The mechanisms underlying this transfer need to be further investigated. Interestingly, advantages of the Val/Val group were no longer observed when the processing demand increased on learning test 2, which required both the consecutive practice of a single parameter and the production of a novel parameter.

The increased information processing demand required on learning test 2 equalized the groups' flexibility capacity. This important finding shows the limits of cognitive flexibility created by dopaminergic levels. This result supports the statement of Tunbridge et al. (2006) about an oversimplification in the notion that an increased/decreased flux of DA in the PFC is directly associated with an increase/decrease in performance. Interactions between the PFC states (e.g., increased phasic dopamine in the Val/Val group) with the nature of the task performed produced different levels of cognitive processing. The combination between random practice and the Val genotype led to increased performance when the maintenance of a single parameter previously practiced in working memory was required (learning test 1). However, this combination did not lead to better processing when the manipulation of previous information to generate a novel parameter was required (learning test 2). More specifically, when a new temporal parameter is outside the range of parameter previously practiced. When the transfer requirements are different from that processed in the final part of acquisition, the expected overlap of brain processes cannot occur

effectively (Lage et al., 2017). This explanative hypothesis of an interaction of type of practice, genotype, and the processing demanded on learning tests should be further investigated in future studies.

Analyses of the groups' oculomotor behavior provide evidences that support the hypothesis that different genotypes of the COMT polymorphism are associated with cognitive stability/flexibility (Rosa et al., 2010). These are unprecedent findings, as previous evidences arose strictly from the groups' performances. Findings of our study indicate that the Val allele carriers actively searched for visual pieces of information that benefit flexibility, while the Met allele carriers search for visual information benefiting stability. Random practice for itself promotes an increased search for information favoring cognitive flexibility (Bicalho et al., 2019; Lelis-Torres et al., 2017). Nonetheless, the analysis of the interaction between type of practice and genotype shows that the PFC dopaminergic state is associated with the type of search for environmental information. During practice, learners dealt with information about (a) the movement pattern to be learned and (b) the trial-to-trial parameters variations. The Val allele carriers predominantly searched for information related to parametrization. This behavior matches their enhanced performance on the acquisition phase and learning test 1.

The active visual search for distinct pieces of information among groups may be associated with the patterns of corticocortical connectivity observed throughout the acquisition phase and learning tests. The Val/Val group had increased coherence levels than the other groups in Theta band during planning. Analyses of spectral power suggest an association of increases in theta band and increased cognitive load (Ryu, Choi, Kim, Kim & Chio, 2016). Moreover, Theta band activity is related to updating in motor planning by means of identification and coding of sensorial information (Brauns et al., 2014). The Val/Val group emphasized their visual search on pieces of information that changed throughout practice. Identification and coding of these pieces of information fed the planning altered at each new trial, leading to a better performance during practice and to a better learning when changes in the practice context are imposed (learning test 1). Despite an increased corticocortical communication of the Val/Val group compared to the other groups on learning test 2, the Val/Val group did not perform better than the other groups.

With regards to the changes in the levels of connectivity among the pairs of electrodes from learning test 1 to learning test 2, only the Val/Val group increased the cortical connectivity in Theta band, planning phase. On the contrary, with regards to the changes in the groups' motor performance from learning test 1 to learning test 2 (Figure 2), the Val/Val group had the greatest decline. These analyses that are speculative and try to explain, at best, some correlations between results, strengthen the hypothesis of transfer-appropriate processing (Bransford et al., 1979). The greatest contextual change on learning test 2 led the Val/Val group to an ineffective processing strategy. In general, the level of cortical connectivity on the pairs of electrodes was increased, but the connectivity load among the different pairs of electrodes was maintained. To the condition of the greatest changes (learning test 2), this change in the pattern of cortical connectivity did not only impair transfer, but also led to worsened performance. In the other groups, there was both increases and decreases of the level of connectivity in different pairs of electrodes, and changes in the connectivity load among the pairs of electrodes. In a descriptive analysis, these groups showed smaller declines in

performance from learning test 1 to learning test 2. Possible causal relationships between the coherence data and the participants' motor performance need to be further investigated.

We found differences among groups in Theta band, execution phase, only on learning tests. During the acquisition phase, the switching of parameters values and the maintenance of a single movement pattern can influence more on the cognitive effort spent during planning than during execution. The greatest effect of variation throughout practice in planning is well-known in studies of practice scheduling (Lage et al., 2017). The level of cortical connectivity during execution was the same among groups on the acquisition phase, despite the Val/Val group presenting differences from the others on the load distribution among the pairs of electrodes. The other groups were more similar to each other (Figure 4). For instance, the coherence level between the F3FC5 and F4FC6 pairs of electrodes differed between the Val/Val group and the other groups. The analysis of the F3P7 and F4P8 pairs of electrodes also exemplify these differences. Regarding the learning tests, the Val/Val group showed increased levels of cortical connectivity, suggesting that in the execution phase, this was the most sensitive group to the changes demanded by the learning tests. The comparison of the frontal pair of electrodes (F3F4), which is linked to the cognitive activity in planning, and the others, shows that during acquisition there is no significant difference between them, while the level of connectivity in the F3F4 significantly increases on learning tests, specially on the test with the greatest demand (learning test 2). Overall, the Val/Val group showed the greatest level of cortical connectivity on both the planning and the execution phase.

The only result that did not confirm our hypotheses was the similar performance of the Met/Met group to the others in the performance and learning of the movement pattern. Studies using cognitive tasks such as Malloy Diniz et al. (2013), Nolan et al. (2004), and Rosa et al. (2010), showed greater cognitive stability of the Met/Met group. However, studies investigating motor learning and performance have conflicting results (Baetu et al., 2015; Krause et al., 2014; Noohi et al., 2014, 2016; Witte et al., 2012). The main cause of these divergences seems to be the nature of the motor tasks assessed in these studies. Nogueira et al. (2019) pointed out that characteristics of the task are central in the study of the COMT Val158Met polymorphism. For instance, with regards to motor sequence learning, the number of sequences to be learned and the scheduling of tasks (e.g., in random or blocked practice) could be of major importance for the benefits of carrying Met or Val alleles. When both stability and flexibility are assessed in a single task, such as in our study, the oculomotor behavior of the Met/Met group is different from the others. Visual scanning to search for information that feeds the processes of motor planning and execution emphasized pieces of information related to the movement pattern. However, this behavior did not lead to a better motor learning and performance in this dimension of the skill. Possibly, the trial-to-trial parameter switches disrupted the intricated process involving the stabilization and maintenance of relevant information in working memory. To better understand this relationship between the Met allele and stability, we suggest, such as Nogueira et al. (2019), that future studies investigate the role of the COMT polymorphisms in practice scheduling. Constant practice, of repetitive nature, could favor learning of the Met allele carriers, while random practice, of varied nature, could favor learning of Val allele carriers. Finally, further studies should try to balance the number of male and females in each group and apply a pre-test, aspects that are limitations of this research. In studies with ex post facto design, there is no manipulation of an independent variable. The groups

can be different from the beginning since they are different in their essence. However, a pre-test can clarify the groups differences in the initial stage of learning.

5 Conclusion

The findings of this study show an association between the COMT Val158Met polymorphism and motor learning. The Val allele is associated with a better performance and learning of the dimension of the skill that requires trial-to-trial changes. Cognitive flexibility promoted by increased phasic dopamine transmission is likely the mechanism involved in this enhanced motor learning. The genotypic characteristics lead to different patterns of visual scanning in the search for information that feeds the processes of motor planning and execution. In the basis of this process, a greater cortical connectivity is associated with the Val allele due to its updating of the motor planning by means of identification and coding of sensorial information. Suggestions to future studies were presented. Combined investigation of the behavioral, electrophysiological and molecular levels of analysis indicated that mechanisms related to motor stability and flexibility involved in skilled behavior are related to the learners' genetic and neurobiological characteristics.

Acknowledgements

We would like to thank Victor Hugo Martins Leme for drawing and designing our figure 1.

Funding

This study was supported by Fundação de Amparo à Pesquisa do Estado de Minas Gerais (FAPEMIG) (grant APQ-03305-15).

Conflict of Interest Statement

There are no conflicts of interest.

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Figures Captions

Figure 1 Procedures Designer. (A) Experimental setup, (B) the sequence of keys pressed (K2...K4), the relative criteria segment ratios (22.2% key 2-8, 44.4% key 8-6 and 33.3% key 6-4) and total criteria movement times (700, 900, and 1,100 ms), (C)

electrodes of the frontal areas (F3 and F4), secondary motor areas (FC5 and FC6) and parietal area (P7 and P8). The arrows indicate the combination of electrodes to the coherence analysis and the offline synchronization of data from the motor task and EEG by a Matlab algorithm, (D) the processing technique used to analyze gaze and quantify the amount of KR and task goals screened by individuals. AOI – Areas of Interest, EEG – Electroencephalography.

Figure 2 Motor performance. Mean and ± SD values of (A) absolute and (B) relative errors over the blocks of trials during the acquisition phase (bl1...10), learning test 1 (Lt1) and learning test 2 (Lt2).

Figure 3 Total dwell time analyzes. Mean and ± SD values of total dwell time (TDT) in seconds over relative (R) and absolute (A) information available on the screen for both (A) KR and (B) goals. TDT of the first and last blocks were analyzed during both feedback and planning periods for the Val/Val, Met/Met, and Val/Met groups.

Figure 4 Corticocortical communication analyzes. (A) and (C) Mean and ± SD values of coherence for each moment (planning or execution) in Theta band. (B) and (D) Modifications of Coh throughout blocks of the acquisition phase and learning tests of the groups Val/Val, Met/Met, and Val/Met in Theta band during planning and execution. Results of the groups Val/Val, Met/Met, and Val/Met are represented from top-down respectively. Warm and cool colors represent high and low coherence, respectively. COH – Coherence.