Modulating Effect of COMT Val^{158}Met Polymorphism on Interference Resolution during a Working Memory Task

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Abstract

Genetic variability related to the catechol-O-methyltransferase (COMT) gene has received increasing attention in the last 15 years, in particular as a potential modulator of the neural substrates underlying inhibitory processes and updating in working memory (WM). In an event-related functional magnetic resonance imaging (fMRI) study, we administered a modified version of the Sternberg probe recency task (Sternberg, 1966) to 43 young healthy volunteers, varying the level of interference across successive items. The task was divided into two parts (high vs. low interference) to induce either proactive or reactive control processes. The participants were separated into three groups according to their COMT Val^{158}Met genotype [Val/Val (VV); Val/Met (VM); Met/Met (MM)]. The general aim of the study was to determine whether COMT polymorphism has a modulating effect on the neural substrates of interference resolution during WM processing. Results indicate that interfering trials were associated with greater involvement of frontal cortices (bilateral medial frontal gyrus, left precentral and superior frontal gyri, right inferior frontal gyrus) in VV homozygous subjects (by comparison to Met allele carriers) only in the proactive condition of the task. In addition, analysis of peristimulus haemodynamic responses (PSTH) revealed that the genotype-related difference observed in the left SFG was specifically driven by a larger increase in activity from the storage to the recognition phase of the interfering trials in VV homozygous subjects. These results confirm the impact of COMT genotype on inhibitory processes during a WM task, with an advantage for Met allele carriers. Interestingly, this impact on frontal areas is present only when the level of interference is high, and especially during the transition from storage to recognition in the left superior frontal gyrus.

Keywords: COMT gene – Working memory – fMRI – Cognitive control

1. Introduction

In the last two decades, several lines of evidence have suggested that the neurotransmitter dopamine (DA) plays an important role in cognitive functions associated with prefrontal activity (Braver & Cohen, 1999; Cropley et al., 2006; Mattay et al., 2002). The study of the influence of DA on cognition in healthy populations appears particularly relevant given the long hypothesized role of DA in schizophrenia (Carlsson et al., 2000), a pathology that is well known to be associated with cognitive impairments (in particular in the executive domain). In that general context, genetic variability related to the catechol-O-methyltransferase (COMT) gene has received increasing attention as a potential modulator of executive functioning (Witte & Flöel, 2012). The human COMT gene codes for the major enzyme involved in the metabolic degradation of released DA. This gene, located on the long arm of chromosome 22q11 (Mannisto & Kaakkola, 1999), contains a single-nucleotide polymorphism (SNP) in codon 158 ($Val^{158}Met$) that affects the enzyme's activity (Chen et al., 2004; Lachman et al., 1996) in the frontal cortices (Karoum et al., 1994). A transition of guanine to adenine in this SNP (rs4680) results in a valine-to-methionine substitution. Consequently, there are three different COMT genotypes (GG, GA, AA), corresponding respectively to Val^{158}/Val^{158} (VV), Val^{158}/Met^{158} (VM) and Met^{158}/Met^{158} (MM) genotypes, each of which is associated with different COMT enzymatic activity. The enzyme resulting from the Met^{158} variant is significantly less active than the Val^{158} enzyme, potentially resulting in a greater synaptic DA level in frontal cortices (Chen et al., 2004; Lotta et al., 1995).

The impact of the COMT gene in modulating high-level cognitive processes and their neural substrates has been reported in various studies (for a review, see Witte & Flöel, 2012). However, this impact, particularly on behavioural performance, was frequently observed in experiments using multi-compound executive tasks (e.g., the Wisconsin Card Sorting Test; Barnett et al., 2007). According to Miyake et al. (2000; see also Miyake & Friedman, 2012), there are at least three essential but separable executive functions: (1) information updating and monitoring in working memory (WM), (2) mental set shifting, and (3) inhibition of prepotent responses. In the present work, we focused on inhibition processes, and more precisely on interference resolution mechanisms at the level of working memory representations. Specifically, we were interested to determine how the COMT gene modulates the implementation of different form of cognitive control strategies (proactive and reactive; Braver et al., 2007; see below) in a working memory task involving interference resolution processes.

At present, the few studies that explored the effect of COMT polymorphism on specific executive processes were interested by updating and inhibition processes. The updating process is classically defined as the ability to continuously modify the content of working memory (WM) based on newer incoming information (Collette et al., 2006). Studies exploring the influence of COMT polymorphism on this process have produced quite reliable results. For example, using a 2-back WM task, Egan et al. (2001) showed that the number of Val alleles was positively linked to the recruitment of the dorsolateral prefrontal cortex (DLPFC) and cingulate cortex. Similarly, Mattay et al. (2003) found more activity in the left middle frontal gyrus (MFG) in VV individuals (compared to MM individuals) when they had to perform 2-back and 3-back tasks. Finally, Bertolino et al. (2008) showed a negative relationship between the number of Met alleles and right DLPFC activity during a 1-back task. These results strongly suggest that COMT $Val^{158}Met$ polymorphism impacts DLPFC responses during updating. Specifically, the physiological brain response in the bilateral DLPFC appeared more efficient in Met allele carriers (by comparison to VV homozygous persons) when information had to be continuously updated in WM.

With regard to COMT polymorphism's influence on the neural substrates of conflict/interference resolution processes, it appears that carriers of Val alleles are characterized, at a similar level of performance, by greater recruitment of cingulate and prefrontal areas during inhibitory tasks, reflecting a less efficient physiological task-related response (Blasi et al., 2005; Congdon et al., 2009; Ettinger et al., 2008; Jaspar et al., 2014b). In a recent study (Jaspar et al., 2014a), we also explored the effects of COMT genotypes on various kinds of cognitive control using an inhibitory task (the Stroop task; Stroop, 1935). Cognitive control refers to the ability to flexibly adjust behaviour depending on situational demands and changes in the environment. According to the Dual Mechanism of Control (DMC) theory (Braver et al., 2007), a distinction should be made between the proactive and reactive forms of control. The DMC model considers that a main function of controlled processes in WM is to maintain task context and goals. In the case of interference resolution, proactive control refers to a sustained form of control that specializes in interference prevention and anticipation, whereas reactive control detects and resolves interference when it occurs. Consequently, one strategy should be favoured over the other depending on whether there is a high or low number of interfering events in the environment. The relevance of the distinction between these two control strategies has been reinforced by results of between-group studies in different populations as children (Chatham et al., 2009), older adults (Braver et al., 2001) or schizophrenic individuals (Barch et al., 2001). For example, using the AX-CPT task, Braver et al. (2001) reported a specific impairment of proactive processing in elderly. Precisely, they administered the task to young and old participants in contexts varying in terms of degree of interference. They reported a specific deficit in elderly during the context implying the higher level of interference. That result strongly suggests that the cognitive control strategy used to treat a same stimulus is dependant of the context, and therefore could be the object of inter-individual differences within a same population. Proactive and reactive control mechanisms are also supposed to be clearly dissociable in terms of cerebral networks involved (Braver, 2012; Braver et al., 2007; De Pisapia & Braver, 2006). Proactive control would be underlined by the ability to actively sustain inputs in lateral PFC while reactive control processes would be associated with transient activations within the lateral PFC, but also the anterior cingulate cortex (ACC). Finally, Braver et al. (2007) proposed that these two mechanisms should differ in the involvement of the dopaminergic system. They assumed that sustained activity in the PFC requires a phasic dopaminergic-mediated gating signal. Consequently, according to these authors, only proactive control processes would be dependent of the midbrain dopaminergic system. Back to the COMT Val^{158}Met polymorphism and according to the DMC model, Met allele carriers' individuals should benefit from their higher level of DA within the PFC when the context requires a sustained brain activity. In that sense, we recently reported that, in MM individuals, proactive control processes during an inhibitory task were linked to decreased sustained brain activity in the left MFG and increased activity in the anterior cingulate cortex (ACC) (Jaspar et al., 2014a).

In the present study, we wanted to examine the modulating effect of COMT Val^{158}Met polymorphism on interference resolution during a WM task. We used a modified form of the Sternberg probe recency task (Sternberg, 1966). In that task, each trial starts with a set of items presented for a short period of time. After a brief delay, a single probe item is displayed. Participants are instructed to indicate if this probe belongs (positive probe) or not (negative probe) to the last set of items presented. This WM task allows researchers to increase the level of interference associated with negative probes by presenting the current probe in the memory set of the prior trial. These interfering trials are generally called 'recent negative' (RN), in opposition to 'non-recent negative' trials (NN), in which no probe-related

interference is induced by the previous memory set. As a whole, this task requires to update information in WM (Wager & Smith, 2003), but also, for the RN trials, to inhibit a prepotent response resulting from the familiarity between the current probe and the previous target set of items. Therefore, consistent with the unity/diversity framework of executive functioning (Miyake et al., 2000), inhibition and updating processes would be conjointly involved in stimuli processing during the task. These two functions might be regulated by common core cognitive control processes (Cooper, 2010), namely WM mechanisms responsible for task context and goals maintenance (Braver et al., 2007). Classically, the interference effect in the task is characterized by slower reaction times (RTs) for RN than NN trials (D'Esposito et al., 1999; Jonides et al., 1998). The neural substrates of this interference effect were localized in the left prefrontal cortex (PFC) (Jonides et al., 1998), specifically during the recognition period (D'Esposito et al., 1999). In the last decade, these two experiments have been replicated several times, and these replication studies highlighted the role of the left inferior frontal gyrus (IFG) in interference resolution (Badre & Wagner, 2005; Mecklinger et al., 2003; Nelson et al., 2003; Postle & Brush, 2004). Furthermore, these studies also suggested the existence of a larger bilateral network associated with inhibitory processes, including the intraparietal sulcus, the precuneus and the right lateral prefrontal cortex (Jonides & Nee, 2006). Finally, Burgess and Braver (2010) adapted this task to assess the neural substrates of the interference effect in situations requiring either proactive or reactive cognitive control processes. When interference expectancy was high (proactive condition), they observed an increase of cortical activity in the left MFG for RN trials (compared to NN trials) during probe recognition. In situations of low interference expectancy (reactive condition), they reported the recruitment of a large fronto-parietal network for RN trials (again compared to NN trials), also during probe recognition.

1.1. Aim of the Study and A Priori Hypotheses

As previously stated, the general aim of the study was to determine whether COMT Val^{158}Met polymorphism has a modulating effect on the brain regions underlying interference resolution during a WM task. We were also interested in investigating whether this potential effect of COMT genotype differs depending on whether the task requires proactive or reactive control to resolve interference. Consequently, a modified version of the Sternberg probe recency task (Sternberg, 1966), implemented to induce either proactive or reactive control strategies, was administered to healthy young individuals genotyped for the COMT Val^{158}Met polymorphism.

Our predictions were as follows. First, from a behavioural point of view, we did not expect any genotype-related differences. Indeed, even though COMT genotype effects have been shown in different multi-compound executive tasks (Barnett et al., 2007; Bruder et al., 2005; Caldu et al., 2007; Egan et al., 2001; Malhotra et al., 2002; Minzenberg et al., 2006; Rosa et al., 2004; Roussos et al., 2008), the advantage of Met allele carriers reported in these studies is no longer observed when tasks involve more specific cognitive processes (for example, in WM tasks such as the n-back task) (Bertolino et al., 2008; Caldu et al., 2007; Egan et al., 2001; Mattay et al., 2003). If, as expected, we observed an absence of behavioural differences between genotypes, the observation of increases of PFC activity in one group will be considered as the reflection of compensatory mechanisms set up to perform the task in the most efficient way possible. On this basis, we predicted, at the brain level, a less efficient cortical response to interference in VV homozygous individuals, especially in the left PFC but also in the right PFC. Indeed, independently of any genetic considerations, the interfering component of the Sternberg probe recency task (Sternberg, 1966) was previously found to be associated with left PFC activity (mainly in the left IFG;

Badre & Wagner, 2005; Burgess & Braver, 2010; D'Esposito et al., 1999; Jonides et al., 1998; Mecklinger et al., 2003; Nelson et al., 2003; Postle & Brush, 2004). Activation in a similar region was also observed in studies considering the impact of COMT genotype on updating and inhibitory functions, with Met allele carriers showing lesser recruitment of the left prefrontal cortex for the same level of performance (Bertolino et al., 2008; Caldu et al., 2007; Egan et al., 2001; Jaspar et al., 2014a; Jaspar et al., 2014b; Mattay et al., 2003). Together, these elements led us to hypothesize that VV homozygous people should recruit the bilateral PFC more extensively in response to interference during the probe recency task. Considering the dopaminergic hypothesis of the DMC account (Braver et al., 2007), we expected these genotype-related differences to be observed only in the proactive condition. Indeed, Braver et al. (2007) hypothesized that the ability to actively sustain inputs in lateral PFC requires a phasic dopaminergic-mediated gating signal occurring at the time when contextual cues are presented. Without such gating signal, the PFC can only be transiently activated, which leads to a reactive form of cognitive control. In others words, only proactive control processes would be dependent of the midbrain dopaminergic system. Finally, our previous results had shown that VV homozygous individuals increased frontal activity related to interference during reactive control processes (Jaspar et al., 2014a; Jaspar et al., 2014b). However, as genotype-related discrepancies during reactive control were localized in the right inferior frontal operculum, an area not classically related to interference resolution in the Sternberg probe recency task (Burgess & Braver, 2010; D'Esposito et al., 1999; Jonides et al., 1998), we did not expect to observe group differences during this condition.

2. Methods

2.1. Ethics Statement

The study was approved by the Ethics Committee of the Faculty of Medicine of the University of Liège. In accordance with the Declaration of Helsinki, all participants gave their written informed consent prior to their inclusion in the study.

2.2. Participants

Sixty-nine right-handed native French-speaking young adults, aged from 18 to 30, with no diagnosis of psychological or neurological disorders, were recruited from the university community. Each participant was screened for any physical or medical condition that could prevent an MRI session. Through DNA screening, our sample was separated into three groups according to their COMT genotype: 22 homozygous Val/Val (VV), 17 homozygous Met/Met (MM) and 30 heterozygotes Val/Met (VM) subjects were recruited. Fifteen subjects were selected from each group in order to match for gender ($F(2,40) = 1.09$; $p = .34$), age ($F(2,40) = 2.63$; $p = .08$) and intelligence level ($F(2,40) = 0.12$; $p = .89$), assessed using Raven's progressive matrices test (Raven, 1983) (see Table 1). Two of the 15 MM volunteers were discarded from the analyses for excessive movements in the MRI scanner during the task (minimum 10 movements of 1 cm or more for these two volunteers during at least one of the two scanning sessions).

[INSERT TABLE 1]

2.3. Genotyping

Genomic DNA was extracted from blood samples using a MagNA Pure LC Instrument. The DNA sequence of interest was amplified by the Polymerase Chain Reaction in a final volume of 50 µl containing 0.6 µM of each primer (Thermo Scientific), 0.5 µl Faststart Taq DNA Polymerase (Roche Diagnostics), 0.8 mM of each deoxynucleotide triphosphate (Roche Diagnostics) and 100 ng of genomic DNA. After 10

minutes of denaturation at 95°C, samples underwent 35 cycles consisting of denaturation (95°C, 30 s), annealing (60°C, 40 s) and extension (72°C, 30 s), followed by a final extension of 7 minutes at 72°C. The amplified DNA then underwent a pyrosequencing reaction (Pyromark Q96 Vacuum Workstation, PSQ 96MA, Pyromark Gold Q96 Reagents, Qiagen). The sequences of primers used are available upon request.

2.4. Materials and Procedure

An adapted form of Sternberg's item-recognition short-term memory task (Sternberg, 1966) was used for this experiment. Each trial was composed of three successive phases: (1) an encoding phase, during which a set of four consonants to memorize was presented for 1.5 s; (2) a storage phase, during which the set had to be maintained in memory for a short period (3 s); (3) a recognition phase, during which a probe letter was presented for a maximum of 1.5 s. Participants were instructed to decide as quickly and accurately as possible if that probe letter belonged to the last group of four consonants presented. The interstimulus interval (ISI) consisted in the presentation of a fixation cross in the centre of the screen for 1.5 s.

There were four different trial types defined by the nature of the probe (see Figure 1): (1) recent negative trials (RN), where the probe did not correspond to any letter in the current target set (correct answer is 'no') but did match a letter from the previous target set; (2) non-recent negative trials (NN), where the probe did not correspond to any letter in the current target set (correct answer is 'no') or in the previous one; (3) recent positive trials (RP), where the probe corresponded to a letter in the current target set (correct answer is 'yes') and also to a letter in the previous one; and (4) non-recent positive trials (NP), where the probe corresponded to a letter in the current target set (correct answer is 'yes'), but did not match any letter in the previous target set. For the four kinds of stimuli, we avoided the appearance of the probe letter in the N-2 and N-3 trials.

[INSERT FIGURE 1]

In order to induce specifically proactive or reactive control processes during the task, two different conditions were created, each being administered in a separate fMRI session. Both parts of the task were composed of 10 blocks of 19 trials. The difference between those two parts (or contexts) resided in the number of RN and NN trials used in each block. In the mostly incongruent context (MI context), associated with a high level of interference and thus requiring the implementation of proactive control to perform the task efficiently, the blocks contained 10 RN, 3 NN, 3 RP and 3 NP trials. In the mostly congruent context (MC context), associated with a low level of interference, and thus necessitating only reactive control when interference was encountered, the proportion of RN and NN trials was reversed. Both contexts were preceded by four examples just before the beginning of the test. The order of presentation of the two parts of the task was pseudo-randomized such that an equal proportion of volunteers in all three groups started with the MI or MC context.

The task was projected on a screen that participants viewed through a mirror located on the MRI scanner's head coil. Participants responded by pressing keys on an MRI-compatible keyboard. Both RTs and accuracy were recorded.

2.5. Behavioural Data Analyses

All behavioural data analyses were conducted with a significance level set at $p < .05$. Repeated measures analyses of variance (ANOVAs) were run on the median RTs and accuracy data (errors and non-responses), with task context (MI, MC) and item type (RN, NN) as repeated measures factors. Group was

used as the independent variable. Given our specific interest here in the interference effect (RN – NN), we did not include positive items (RP and NP) in these ANOVAs.

2.6. fMRI Acquisition and Analyses

Functional and structural MRI images were acquired on a 3T head-only scanner (Magnetom Allegra, Siemens Medical Solutions, Erlangen, Germany) operated with the standard transmit-receive quadrature head coil. For anatomical reference, a high-resolution T1-weighted image was acquired for each subject: 3D MDEFT (Deichmann et al., 2004); TR = 7.92 ms, TE = 2.4 ms, TI = 910 ms, FA = 15°, FoV = 256 x 224 x 176 mm^3, 1 mm isotropic spatial resolution. Multislice T2*-weighted functional images were acquired with a gradient-echo echo-planar imaging sequence using axial slice orientation and covering the whole brain (34 slices, FoV = 192 x 192 mm^2, voxel size 3 x 3 x 3 mm^3, 25% interslice gap, matrix size 64 x 64 x 34, TR = 2040 ms, TE = 30 ms, FA = 90°). The three initial volumes were discarded to avoid T1 saturation effects. Between 1000 and 1050 volumes were acquired for each part of the task. Finally, a gradient-recalled sequence was applied to acquire two complex images with different echo times (TE = 4.92 and 7.38 ms, respectively) and generate field maps for distortion correction of the echo-planar images (EPI). The other acquisition parameters were TR = 367 ms, FoV = 230 x 230 mm^2, 64 x 64 matrix, 34 transverse slices (3 mm thickness, 25% interslice gap), flip angle = 90°, bandwidth = 260 Hz/pixel.

Data were preprocessed and analysed using SPM8 (Wellcome Trust Centre for Neuroimaging, http://www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB 7.5.0 (Mathworks Inc., Sherborn, MA). EPI time series were corrected for motion and distortion using Realign and Unwarp (Andersson et al., 2001) together with the FieldMap toolbox (Hutton et al., 2002) in SPM8. Images of each individual participant were first realigned (motion-corrected). After this realignment, we spatially coregistered the mean EPI image to the anatomical MRI image and coregistration parameters were applied to the realigned BOLD time series. Individual anatomical MRIs were spatially normalized into the MNI space (Montreal Neurological Institute, http://www.bic.mni.mcgill.ca), and the normalization parameters were subsequently applied to the individually coregistered BOLD times series, which was then smoothed using an isotropic 8-mm full-width at half-maximum (FWHM) Gaussian kernel.

At the first level, for each participant, BOLD responses were modelled at each voxel, using a general linear model with events convolved with the canonical haemodynamic response function as regressors. Events were divided according to the two contexts (MI and MC) and the four types of items (RN, NN, RP and NP). These eight regressors were modelled as event-related responses without separating the different trials' phases (encoding, storage, recognition). Consequently, event duration was set at 7.5 s [encoding = 1.5 s; storage = 3 s; recognition = 1.5 s; ISI = 1.5 s]. The logic to include the ISI in events modelling was to increase analyses sensitivity to the hypothesized sustained PFC activity during the proactive condition. Incorrect trials and no responses in each context were modelled as two separate regressors. The design matrix also included the realignment parameters of each session to account for any residual movement-related effect. A high-pass filter was implemented using a cut-off period of 128 s in order to remove the low-frequency drifts from the time series. After these model specifications, the model's parameters were estimated. The resulting set of voxel values constituted a map of t statistics, SPM[T]. Linear contrasts were then created to assess the interference effect (RN – NN trials) in the entire task but also in the MI and MC contexts separately. The corresponding contrast images were smoothed using an isotropic 2-mm FWHM Gaussian kernel.

At the second level (random effect analysis), we used individual contrast images to specifically examine brain activity related to the interference effect (RN – NN) in both contexts simultaneously and brain activity related to the interference effect in the MI and MC contexts separately. In the first step, we centred our attention on the neural activity common to the three genotype groups for the effects of interest (RN – NN in the whole task, MC context and MI context). In the second step, we focused on genotype-related differences. T-test comparisons were performed between VV, VM and MM groups. All these analyses were conducted within SPM8 thresholded at $p < .001$, uncorrected. The extent threshold was set to 10 contiguous voxels. In addition, we repeated these genotype comparison analyses using a Met-dominant model, such that all Met carriers were compared to VV homozygous individuals (VV vs. MM and VM together). This genotype model was chosen based on previous fMRI findings during a WM task showing that this model is the most effective in that context for highlighting genotype effects on cerebral activity (Dumontheil et al., 2011). The two groups created for these analyses were also matched in terms of gender, age and intelligence level (see Table S1 in Supplemental Data). We will only consider as relevant for further discussion genotype differences that were initially found in the first analyses (comparisons of each genotype to the two others) and confirmed by the second set (comparisons based on the Met-dominant model). Nevertheless, in order to confirm our a-priori hypothesis that a Met-dominant model was better to highlight genotype effects, we also ran the analyses using a Val-dominant model (MM vs. VV and VM together). Genotypic differences associated to the Val-dominant model were considered as relevant for discussion when also observed in the "classic" between-groups comparisons. Again, the two groups created for these analyses were matched in terms of gender, age and intelligence level (see Table S2 in Supplemental Data).

Recently, some studies have tackled the question of potential sexually dimorphic effects of COMT on brain activations (Sannino et al., 2014; White et al., 2014). To exclude from our interpretations the confounding factors represented by sex, we also conducted the fMRI analyses adding sex as a covariate. Anticipating the next section, consideration of sex did not modify the results.

Finally, we were also interested in analysing the time course of activation in the areas found to be differently activated in our group comparisons. The logic was to test whether genotype-related differences in cerebral activity for the interference effect were specifically associated with one of the phases (encoding, storage, recognition and ISI) of each trial. Consequently, for each participant and each target region, we extracted the peristimulus hemodynamic response (PSTH) during RN and NN trials at four different time points (0.25 s after the beginning of each phase) using a finite impulse response (FIR) model. These four time points were selected to assess the FIR response just after a consequent change in the task cognitive requirement. Then, still at the individual level, for each area of interest and at each time point, we subtracted NN from RN FIR values in order to obtain an FIR interference index (FIR_II). Finally, for each area, we conducted an ANOVA on FIR_II with phase (encoding, storage, recognition, ISI) as a repeated measure and group (VV vs. Met allele carriers) as independent variable. These PSTH analyses focused only on group discrepancies in the MI condition. In fact, we did not observe any genotype-related differences in brain activity for the interference effect during the reactive condition.

3. Results

3.1. Behavioural Results

We conducted a repeated measures 2 (context) x 2 (item) ANOVA on median RTs for correct responses with group as an independent variable. First, we observed a main effect of item [$F(1,40) = 8.74$;

p = .005]. As expected, slower RTs were observed for RN than NN items (see Figure 2a). We did not observe any effect of context [F(1,40) = 0.05; p = .82] or group [F(2,40) = 0.16; p = .85]. There were no significant interactions between item and context [F(1,40) = 0.89; p = .35], between item and group [F(2,40) = 2.42; p = .10] or between context and group [F(2,40) = 0.10; p = .90] (see Figure 2a and 2b).

Then, we conducted a repeated measures 2 (context) x 2 (item) ANOVA on item accuracy with group as an independent variable. Again, we observed a significant effect of item [F(1,40) = 8.09; p < .007], with better performance for NN items than RN items (see Figure 2c). We did not observe an effect of context [F(1,40) = 2.05; p = .16] or group [F(2,40) = 0.28; p = .76]. There were no significant interactions between item and context [F(1,40) = 2.39; p = .13], between item and group [F(2,40) = 1.07; p = .35] or between context and group [F(2,40) = 0.09; p = .91] (see Figure 2c and 2d).

[INSERT FIGURE 2]

Given that a Met-dominant model has been used in fMRI analyses, we performed these ANOVAs on RTs and accuracy with Met allele carriers grouped together. The results obtained are similar to those mentioned above. This is also true when analyses were conducted using a Val-dominant model (see Supplemental Data for all these additional results).

3.2. fMRI Results

As indicated in the Methods section, fMRI analyses were first conducted by comparing each genotype to the other two separately and then by grouping Met allele carriers together. We will report in the tables and consider as relevant for further discussion only genotype-related differences that were initially found in the first analyses (comparisons of each genotype to the other two) and confirmed by the second set (comparisons based on a Met-dominant model).

Neural substrates of the interference effect for the task as a whole. The general interference effect (RN – NN) in the entire sample of participants did not reveal any significant pattern of activation at the brain level. As well, considering both kinds of group comparisons, no group differences were observed for this effect except higher activity in the right precuneus for VM heterozygotes individuals than in MM individuals (see Table S3 in Supplemental Data). The same results were observed when sex was used as a covariate in the analyses.

Neural substrates of the interference effect in the reactive control condition. We did not observe any significant pattern of activity for the interference effect (RN – NN) during the MC blocks (see Table S4 in Supplemental Data for deactivation pattern). Nor did we observe any genotype differences for the interference effect specific to the MC context, using 'classic' three-group comparisons or comparisons based on a Met-dominant model. Using sex as a covariate, only two areas were observed differently activated with the 'classic' three-group comparisons (see Table S5 in supplemental data). However, these results were not confirmed by the analyses based on a Met-dominant model.

Neural substrates of the interference effect in the proactive control condition. In the whole sample of participants, the right MFG and left inferior parietal lobule appeared more activated for RN (compared to NN) items during the MI blocks (see Table S6 in Supplemental Data). Interestingly, when the pattern of cerebral activity for RN (compared to NN) trials in the MI context was compared for VV, VM and MM participants (see Tables S7 and S8 in Supplemental Data for all results), we observed higher brain activity in the bilateral medial frontal gyrus (MedFG), the left SFG, the left PcG and the right IFG for VV homozygous persons (see Table 2 and Figure 3). These results were confirmed in the analyses conducted using the Met-dominant model (see Table 2). Similar results were observed when sex was used as a

covariate (see Table S9 in supplemental data). As shown by the observation of beta estimates in Figure 3, these group differences appeared to be mainly driven by VV homozygous subjects. This was confirmed by the analysis of the interference effect in each group separately, which revealed significant changes in activity in the above-mentioned brain areas between RN and NN trials in the MI context in VV individuals only (see Table 3).

[INSERT FIGURE 3 AND TABLES 2 AND 3]

Time course of activation related to the interference effect in the proactive control condition. We conducted an ANOVA on FIR_II with phase (encoding, storage, recognition, ISI) as a repeated measure and group (VV vs. Met allele carriers) as independent variable for each frontal region found to be modulated by COMT Val^{158}Met polymorphism in the MI context. We found significant results associated with genotype only in the left SFG (–30 54 28) (see Supplemental Data for additional results). In this region, we first observed a main effect of phase [$F(3,123) = 4.15$; $p = .007$], but no main effect of group [$F(1,41) = 0.15$; $p = .70$]. This phase effect was characterized by a higher FIR_II during recognition than encoding [$F(1,41) = 11.65$; $p = .001$], storage [$F(1,41) = 5.07$; $p = .03$] or ISI [$F(1,41) = 6.33$; $p = .02$] phases. Interestingly, we also observed a significant interaction between phase and group [$F(3,123) = 3.74$; $p = .01$], characterized by a larger increase in FIR_II from the storage to the recognition phase in the VV homozygous group (by comparison to in Met allele carriers) [$F(1,41) = 9.86$; $p = .003$] (see Figure 4).

[INSERT FIGURE 4]

Neural substrates of the interference effect when using a Val-dominant model. When considering the task as a whole or the reactive condition alone, there was no common pattern of activation for the interference effect between the "classic" between-groups comparisons and the Val-dominant analyses. With regard to the proactive condition, we observed that Val allele carriers had a higher brain activity for RN trials (when compared to NN trials) in the right superior temporal gyrus (STG) and IFG (see Table 4). The cluster of voxels observed in the right IFG has the same spatial localization than the one reported in analyses using a Met-dominant model, but is spatially less extended.

[INSERT TABLE 4]

4. Discussion

The general aim of the study was to determine whether COMT Val^{158}Met polymorphism has a modulating effect on the brain cortical areas underlying interference resolution during a WM task, and how this potential effect was associated with the cognitive control processes required by the task.

The results obtained can be summarized as follows. First, independently of COMT genotype, we observed the classical cognitive interference effect associated with the Sternberg task. However, the interfering component of the task was not associated with any significant effect on brain activation. Second, with regard to the influence of COMT Val^{158}Met polymorphism, we did not find, as expected, any effect of the COMT gene on behavioural performance, either for RTs or for response accuracy. At the cerebral level, we detected significant group differences in interference resolution during the proactive condition of the task. By contrast, when considering the reactive condition or the task as a whole, interference resolution in WM was not associated with any genotype-related differences. Group differences observed in the MI context supported our hypotheses: to resolve interference, homozygous VV individuals recruited a frontal network including the bilateral MedFG, the right IFG, the left PcG and the left SFG to a larger extent than Met carriers. Specifically, gene-related differences observed in the right IFG and left PcG and SFG appeared to be mainly driven by neural activity during the trials involving

interference, namely the RN trials. By contrast, differences observed in the bilateral MedFG seemed to be associated with processing of the NN trials. In addition, the study of time course activation patterns in these frontal regions revealed that COMT Val^{158}Met polymorphism influences the time course of activity in the left SFG: we observed a larger increase in activity in this area for RN trials (by comparison to NN) from the storage to recognition phases of the task in VV individuals. Finally, it seems important to emphasize that analyses conducted within the PFC using a Val-dominant model also demonstrated genotype differences in the same right IFG area (VV activity higher than Met allele carriers), but with a less spatial extent. Following Dumontheil et al. (2011), these results strongly suggest that the Met-dominant model is the most appropriate to highlight COMT genotype discrepancies in terms of frontal activity associated with interference resolution at the level of working memory representations.

How can we explain the brain-related absence of interference in our Sternberg task when participants are considered independently of their COMT genotype?

Contrary to the results initially reported by Jonides et al. (1998) and D'Esposito et al. (1999), we did not observe a reliable increase in activity in the left PFC in our participants as a whole.

There are several possible explanations for this discrepancy. First, it could be due to the substantial within-subject variability in the BOLD-fMRI signal, particularly in tasks involving motor responses (Zandbelt et al., 2008). Although this explanation may apply to the studies by Jonides et al. (1998) [N = 7] and D'Esposito et al. 1999 [N = 12], it is not true of more recent studies, in which at least 20 participants were included (Burgess & Braver, 2010; Postle & Brush, 2004). Indeed, the reliability of BOLD activation patterns in block-related and event-related fMRI studies is relatively stable with 20 subjects or more and is not improved by adding more participants (Desmond & Glover, 2002; Murphy & Garavan, 2004).

Second, differences between the proportions of RN and NN items in this study (in the proactive condition: ≈ 53% for RN trials and ≈ 15% for the three other kinds of trials; in the reactive condition: ≈ 53% for NN trials and ≈ 15% for the three other kinds of trials) diverge from those in previous ones. Jonides et al. (1998) and Badre and Wagner (2005) administered equal numbers of the four kinds of trials, and when unequal proportions of the four trial types were reported (Burgess & Braver, 2010; D'Esposito et al., 1998; Mecklinger et al., 2003; Nelson et al., 2003), these proportions differed considerably from those used in the present study. Nevertheless, in Burgess and Braver's study, the difference in proportions between these two kinds of items (RN: 40% vs. NN: 10% in the proactive condition, and the reverse in the reactive one) is almost the same as in our study. However, another distinction between that study and ours is that Burgess and Braver used a regions of interest (ROI) approach, and the ROIs were defined on the basis of meta-analyses identifying networks of regions associated with WM and executive processes. Consequently, their results may be biased toward brain areas associated with more general WM/executive functioning, and not specifically with interference resolution (as in the present study).

Third, population samples differ between studies. Because our main objective was to explore genotype-related effects on the brain substrates for interference resolution and cognitive control, our participants were selected from a larger sample in order to create three COMT-genotype groups (VV, VM and MM) of 15 participants each matched for age, sex and fluid intelligence. However, in Caucasians, VM individuals represent 50% of the general population whereas people homozygous for the Val and Met allele represent approximately 25% each (Hoda et al., 1996; Palmatier et al., 1999). The results we obtained here are mainly driven by the VV homozygous individuals. Thus, it seems plausible that over- or

under-representation of that genotype in a group of participants (particularly with small sample sizes) is likely to modify the results obtained. In that context, we had previously observed that different patterns of brain activity were obtained on a Stroop task depending on whether or not COMT genotype is controlled for (Grandjean et al., 2012; Jaspar et al., 2014a).

Impact of COMT Val^{158} Met Polymorphism on Neural Substrates of Interference Resolution

Although we did not observe an effect of COMT genotype on interference resolution during the reactive condition of the task, we did notice one on the frontal cortices during the proactive condition. Interestingly, some of the areas reported to be more activated in VV homozygous people (right IFG, left SFG and PcG) have been widely associated with the adjustment of behaviour to handle conflicting situations; this result has been found both independently of and in relation to COMT genotype. First, the right IFG has often been associated with the cortical response to conflicting situations (Garavan et al., 1999; Garavan et al., 2002; Konishi et al., 1999; Rubia et al., 2003; for a review, see Aron et al., 2004, 2014), especially during the probe recency task (Mecklinger et al., 2003). In addition, we had previously shown greater transient activity in this region in VV individuals when they had to deal with interfering items in a Stroop task (Jaspar et al., 2014b). As mentioned above, interference resolution in tasks using the Sternberg paradigm was initially associated with the left PFC (D'Esposito et al., 1999; Jonides et al., 1998), and in the last decade, several replications of these experiments have emphasized the role of the left IFG in interference resolution associated with this task (Badre & Wagner, 2005; Mecklinger et al., 2003; Nelson et al., 2003; Postle & Brush, 2004). In addition, some of these studies also linked interference resolution to increased brain activity in the right lateral PFC (Badre & Wagner, 2005; Mecklinger et al., 2003), suggesting the existence of a large bilateral network of frontal regions responsible for the inhibitory process linked to the task (Jonides & Nee, 2006). The left PcG and SFG, where activation was observed in our study, could be part of this PFC network. So, consistently with the literature, our results appear to confirm that individuals who have less DA available in the frontal cortices (VV homozygous group) recruit the frontal structures linked to interference resolution more than Met allele carriers in order to perform the Sternberg probe recency task at the same level of performance. Finally, we also observed more activity in the bilateral MedFG in VV homozygous individuals. However, by contrast to the areas discussed just before, this result appeared mainly driven by a decrease of activity during NN trials. NN trials involve the same cognitive processes than RN trials, except for the interference resolution process. As NN trials are supposed to imply less cognitive mechanisms, the interpretation of the interaction between genotype and interference effect in that area seems very difficult to interpret in the context of the present study.

The results are also in line with the dopaminergic hypothesis of the DMC model (Braver et al., 2007). Braver et al. proposed that proactive and reactive control mechanisms are clearly dissociable in terms the dopaminergic system's involvement. The ability to actively sustain inputs in lateral PFC, as is the case when a proactive control strategy is required, requires a phasic dopaminergic-mediated gating signal to occur when contextual cues are presented. Consequently, according to this model, individuals who carry at least one Met allele should have an advantage due to their higher level of available DA. Given the lack of behavioural differences between groups, we consider the greater PFC recruitment by the VV homozygous group to represent a form of compensatory mechanism, enabling them to resolve interference appropriately and in a proactive manner; this interpretation is congruent with the DMC model. Interestingly, the left-lateralized regions observed to be more activated in VV individuals in the proactive condition are close to those previously reported (in the same population) during tasks involving

updating processes (Bertolino et al., 2008; Caldu et al., 2007; Egan et al., 2001; Mattay et al., 2003), suggesting that these studies may have tapped into common processes. Indeed, Miyake et al. (2000), using variable latent analyses, showed that even though the executive functions of inhibition, updating and flexibility can be considered as independent constructs, the cognitive processes engaged by these three functions share some common features. The authors proposed that this commonality of processes could reflect basic inhibitory abilities (e.g., selective attention) or the need to maintain in working memory the aim and contextual information about the ongoing task. So, in future studies, it will be interesting to assess if these left frontal regions influenced by DA availability can be related more specifically to one or other of these processes.

As a whole, these results are in agreement with the literature. In the absence of behavioural differences, Met allele carriers seem to handle interference during information processing in WM better than VV homozygous individuals, as indicated by their more efficient neural response in frontal areas (namely, lower increase of brain activity). Importantly, PSTH analyses revealed that VV individuals presented a larger increase of brain activity in the left SFG from the storage to the recognition phase of the task. This backs up the idea that the interference effect is mainly expressed in the left frontal cortices at the probe presentation stage (D'Esposito et al., 1999; Postle & Brush, 2004). However, it may be considered surprising that the PSTH analyses revealed genotype-related differences in only one of the three areas mentioned above, as the other two areas have also been found to be associated with interference resolution: the left IFG in various inhibitory processes (Garavan et al., 1999; Garavan et al., 2002; Konishi et al., 1999; Rubia et al., 2003) and the left PcG specifically during the Sternberg probe-recency task (this region includes the left middle ventrolateral prefrontal cortex; cf. Badre & Wagner, 2005). So we would have expected genotype differences in these two regions to be mainly observed at the probe presentation stage. It is possible that the differences observed between genotypes are not expressed in PSTH analyses because of the specific (and relatively sparse) time points used here. Further studies designed to explore the time course of activation in more detail will be necessary to respond to this point.

5. Limitations of the study

Due to the lack of behavioural differences between groups, we discussed genotype discrepancies observed within the PFC as possible compensatory mechanisms allowing the VV homozygous to perform the task efficiently. However, even if our sample size (between 13 and participants/group) is usual and sufficient to observe significant effects in event-related fMRI designs, we cannot reject the hypothesis that the absence of genetic-related behavioral effects is due to a sparse number of participants. Indeed, it has been widely discussed in the literature that larger samples are requested to evidence genetic effects on behavior (e.g., Mattay et al., 2008). Therefore, the absence of behavioral differences could be simply due to a lack of statistical power resulting from our small sample size. Further investigations using the same task design and larger samples would be helpful to state on this issue.

Another limitation to our study was probably the impossibility to specifically test for the effects of sex on brain activity. Indeed, sexually dimorphic effects of COMT at the brain level during executive processing have been very recently reported (Sannino et al., 2014; White et al. 2014). Unfortunately, our sample of participants was not recruited to question this issue. Nevertheless, it must be emphasized that

additional analyses using sex as a covariate led to similar results, suggesting that genotypic differences in brain activity observed during the task are independent of any sex effect.

6. Conclusion

In conclusion, these results strongly support the hypothesis that COMT Val^{158}Met polymorphism has an impact on the neural substrates of interference resolution during WM processing. This influence was expressed in a better physiological response by Met allele carrier. Interestingly, the impact of COMT genotype on frontal areas is only present when the level of interference is high, especially during the recognition phase in the left SFG. This is in agreement with one of our previous studies on the Stroop task (Jaspar et al., 2014a), which also showed that Met allele carriers responded more efficiently when proactive control was required to overcome inhibition. This confirms, as initially suggested by Braver et al. (2007), the importance of dopamine availability for the management of cognitive control processes.

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Table 1: Demographic Variables. Means (standard deviation) for age and intelligence level (IQ), and number of males and females in each group.

	Val/Val (N=15)	**Val/Met (N=15)**	**Met/Met (N=13)**
Age	23.33 (2.16)	24.67 (2.16)	22.92 (2.06)
IQ	54.33 (3.90)	53.93 (2.63)	54.46 (2.18)
Gender (M/F)	8/7	5/10	8/5

Table 2: Interference Effect in Proactive Control Condition – Common Features between Comparisons by Genotype and Comparisons using a Met-dominant model.

Hemisphere	Anatomical region	MNI coordinates			BA	Cluster size	Z score	P value
		x	y	z				
Comparisons by genotype								
VV > MM								
L	Superior frontal gyrus	–36	54	20	10	128	3.76	< .0001
R	Medial frontal gyrus	10	–20	52	6	24	3.29	< .001
L		–12	–14	54	6	1125	3.85	< .0001
R	Inferior frontal gyrus	60	16	30	9	478	3.63	< .0001
		42	32	4	46	484	4.06	< .0001
L	Precentral gyrus	–62	10	14	44	93	3.75	< .0001
		–58	–2	24	6	94	3.38	< .001
VV > VM								
L	Superior frontal gyrus	–30	54	28	10	20	3.35	< .001
R	Medial frontal gyrus	10	–18	58	6	34	3.36	< .001
L		–14	–14	54	6	33	3.56	< .001
R	Inferior frontal gyrus	62	14	28	9	25	3.37	< .001
		46	38	16	46	15	3.25	< .001
L	Precentral gyrus	–62	8	14	44	23	3.43	< .001
		–58	–2	30	6	29	3.23	< .001
Comparisons based on Met-dominant model								
VV > VM & MM								
L	Superior frontal gyrus	–30	54	28	10	173	3.70	< 0.001
R	Medial frontal gyrus	8	–20	54	6	106	3.58	< .001
L		–14	–14	54	6	254	3.92	< .0001
R	Inferior frontal gyrus	62	14	28	9	236	3.72	< .001
		44	36	14	46	194	3.64	< .001
L	Precentral gyrus	–62	10	14	44	315	3.81	< .0001
		–58	–2	28	6	315	3.53	< .001

Note. Local maxima of brain regions showing more transient brain activity for the interference effect (recent negative vs. non-recent negative items) in VV homozygous individuals during MI blocks at a voxel p value < .001 uncorrected.

L/R = left or right; x, y, z: coordinates (mm) in the stereotactic space defined by the Montreal Neurological Institute (MNI); BA = Brodmann Area.

Table 3: Interference Effect in Proactive Control Condition – Specific Activation Pattern of Each Genotype Separately.

Hemisphere	Anatomical region	MNI coordinates			BA	Cluster size	Z score	P value
		x	y	z				
MM homozygous – Activation Nothing								
VM heterozygotes – Activation Nothing								
VV homozygous – Activation								
L	Superior frontal gyrus	–30	54	28	10	108	3.81	< 0.01
R	Medial frontal gyrus	10	–16	58	6	24	3.42	< .001
L		–14	–12	54	6	4	3.19	< .001
R	Inferior frontal gyrus	60	18	30	9	511	3.93	< .001
		42	36	16	46	511	3.45	< .001
L	Precentral gyrus	–60	10	14	44	334	4.01	< .001
		–62	–2	22	6	334	3.64	< .001

Note. Local maxima of brain regions showing more transient brain activity for the interference effect (recent negative vs. non-recent negative items) in VV homozygous individuals during MI blocks at a voxel p value < .001 uncorrected.

L/R = left or right; x, y, z: coordinates (mm) in the stereotactic space defined by the Montreal Neurological Institute (MNI); BA = Brodmann Area.

Table 4: Interference Effect in Proactive Control Condition – Common Features between Comparisons by Genotype and Comparisons using a Val-dominant model.

Hemisphere	Anatomical region	MNI coordinates			BA	Cluster size	Z score	P value
		x	y	z				
Comparisons by genotype								
VV > MM								
R	Inferior frontal gyrus	42	32	4	46	484	4.06	< .0001
R	Superior temporal gyrus	48	-36	10	41	223	4.02	< .0001
VM > MM								
R	Inferior frontal gyrus	38	32	8	46	10	3.29	< .001
R	Superior temporal gyrus	46	-38	6	41	27	3.58	< .001
Comparisons by allele								
VV & VM > MM								
R	Inferior frontal gyrus	42	32	-2	46	158	3.62	< .001
R	Superior temporal gyrus	46	-38	8	41	119	4.10	< .0001

Note. Local maxima of brain regions showing more transient brain activity for the interference effect (recent negative vs. non-recent negative items) in VV homozygous individuals during MI blocks at a voxel p value < .001 uncorrected.

L/R = left or right; x, y, z: coordinates (mm) in the stereotactic space defined by the Montreal Neurological Institute (MNI); BA = Brodmann Area.

Figure 1: Probe recency task: Schematic representation of the four trial types (figure modified from Manard et al., 2014). (1) Recent negative trial: the response is 'no', but the probe did match the previous target set. (2) Non-recent negative trial: the response is 'no' and the probe did not match the previous target set. (3) Recent positive trial: the response is 'yes' and the probe also matched the previous target set. (4) Non-recent positive trial: the response is 'yes' and the probe did not match the previous target set.

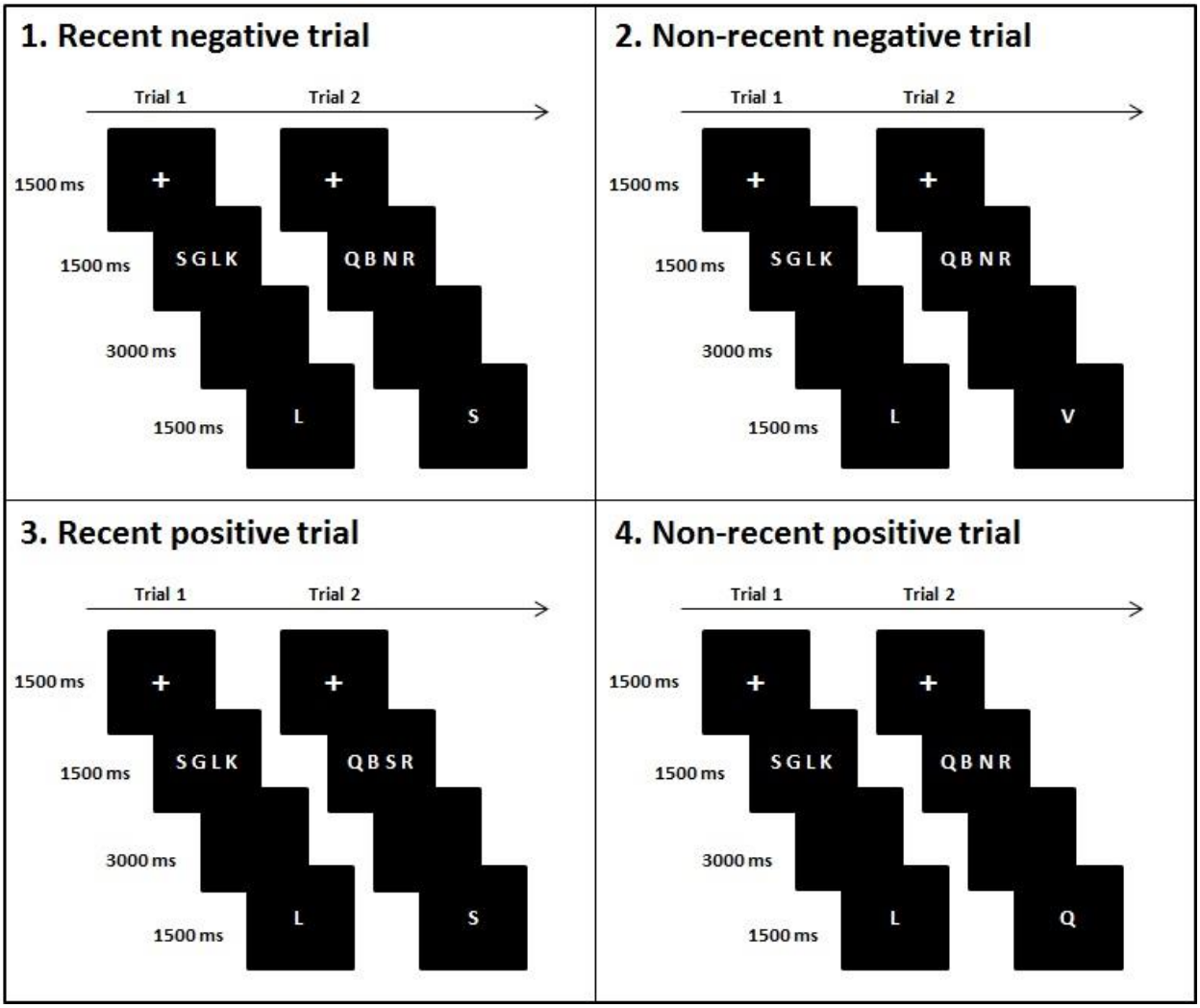


Figure 2: Graphic representation of behavioural results. Median reaction time (ms) for recent negative (RN) and non-recent negative (NN) trials in the whole task (WT), but also separately in the mostly incongruent (MI) and mostly congruent (MC) contexts for **(A)** all subjects together and **(B)** the three groups separately. Mean accuracy (%) for RN and NN trials in the WT, but also separately in the MI and MC contexts for **(C)** all subjects together and **(D)** the three groups separately. Significant results are highlighted with an asterisk (***** means p value < .01).

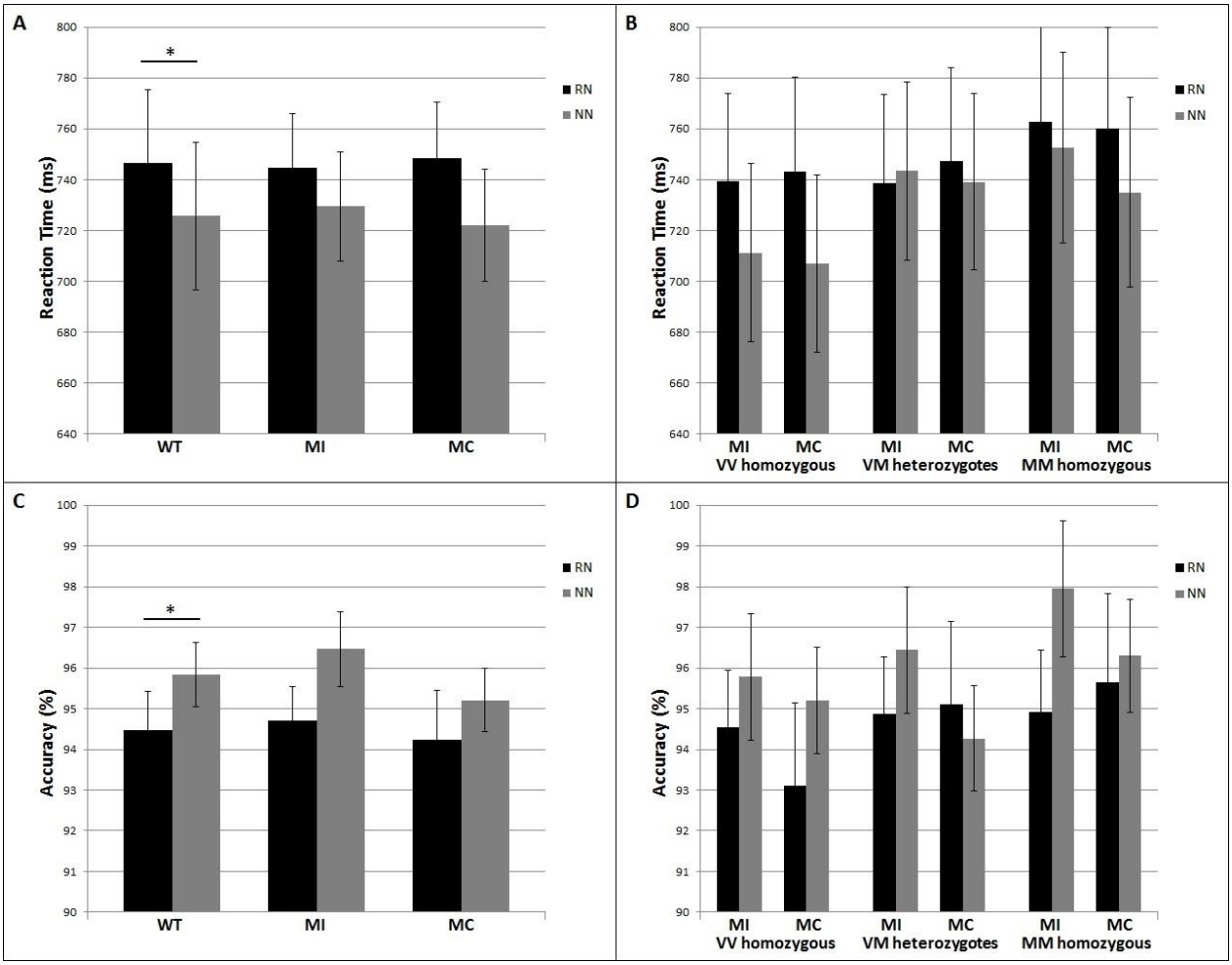


Figure 3: Brain areas involved in proactive interference resolution that are affected by COMT genotype. Brain areas showing higher differential activity between RN and NN in VV homozygous individuals compared to heterozygotes VM and homozygous MM individuals. Top: left and right medial frontal gyrus (MedFG); Middle: left precentral gyrus (PcG) and right inferior frontal gyrus (IFG); Bottom: left superior frontal gyrus (SFG) and right IFG. The regions are displayed on the T1 canonical image implemented in SPM8. Each individual beta estimate represents the mean value of a 27 voxels cube whom the centre is the voxel referenced in the table 2 (MM = Met/Met participants; VM = Val/Met participants; VV = Val/Val participants).

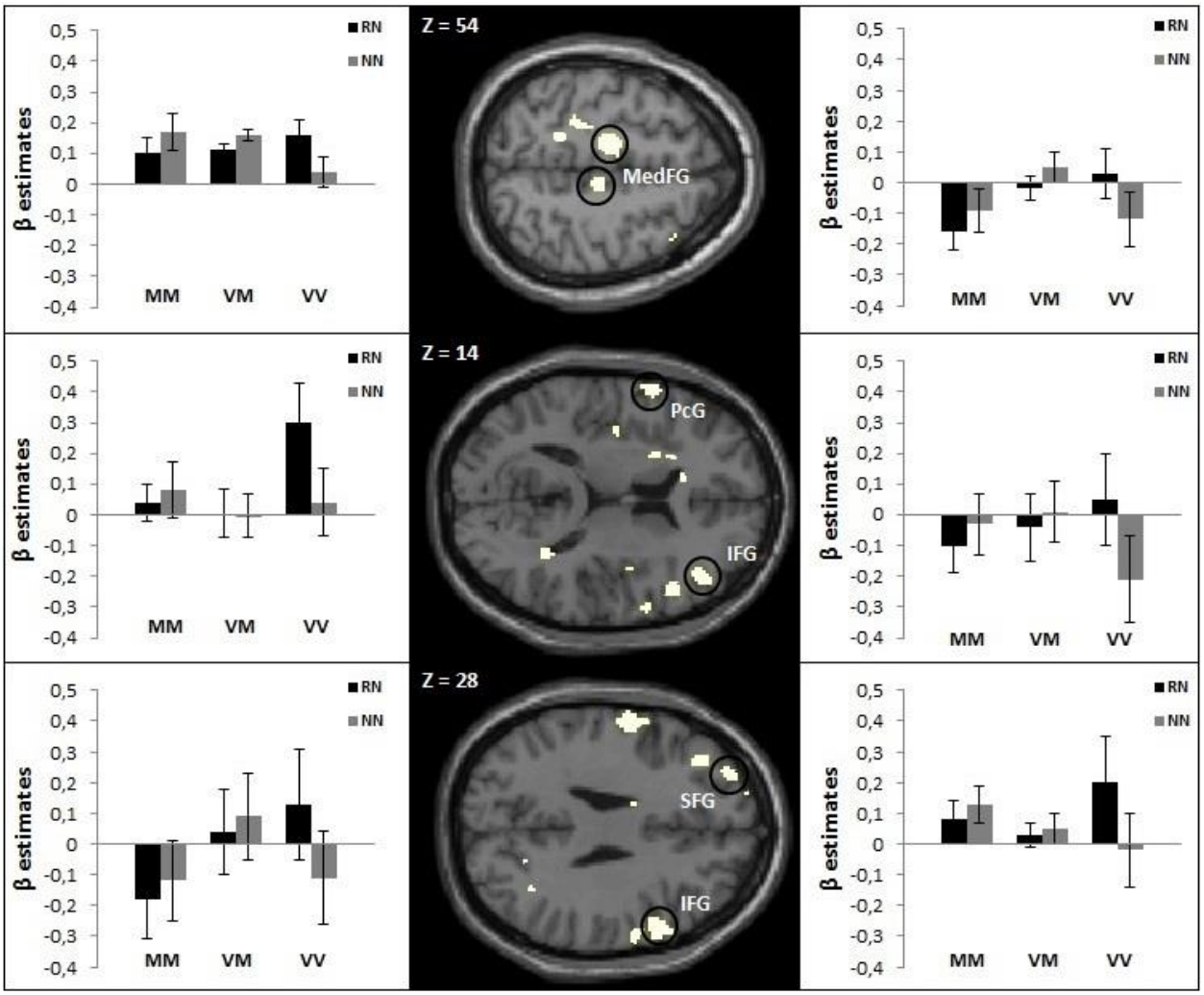
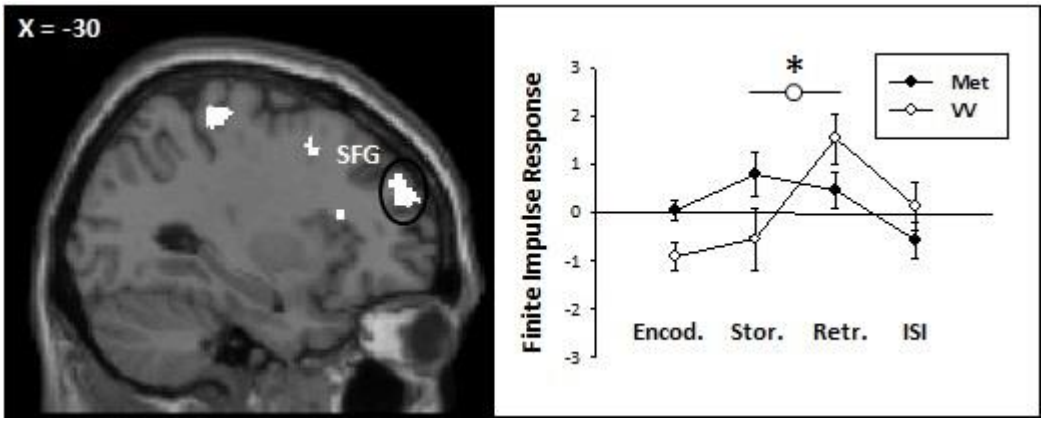


Figure 4: Brain area involved in proactive interference resolution for which the time course of activation is affected by COMT genotype. Finite impulse response observed for RN trials minus NN trials for the two groups of participants (VV = Val/Val participants; Met carriers = VM and MM participants) during the four phases of the task [encoding (Encod.), storage (Stor.), recognition (Rec.) and the interstimulus interval (ISI)]. The region is displayed on the T1 canonical image implemented in SPM8.



Modulating Effect of COMT Val^{158}Met Polymorphism on Interference Resolution during a Working Memory Task

SUPPLEMENTAL DATA

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Methods

fMRI acquisition and analyses

The Met-dominant model used in some fMRI analyses conducted in our study required us to create two groups based on COMT Val^{158}Met polymorphism. These two groups were matched for gender (t = 0.01; p = .98), age (t = 0.73; p = .47) and intelligence level (t = 0.16; p = .87), assessed using Raven's progressive matrices test (Raven, 1983) (see Table S1).

Table S1: Demographic variables. Mean (standard deviation) for age and intelligence level (IQ), number of males and females in each group created based on a Met-dominant model.

	Val/Val (N=15)	**Met carriers (N=28)**
Age	23.33 (2.16)	23.85 (2.26)
IQ	54.33 (3.90)	54.18 (2.40)
Gender (M/F)	8/7	13/15

The Val-dominant model used in some fMRI analyses conducted in our study required us to create two groups based on COMT Val^{158}Met polymorphism. These two groups were matched for gender (t = 1.30; p = .20), age (t = 1.49; p = .14) and intelligence level (t = -0.33; p = .74), assessed using Raven's progressive matrices test (Raven, 1983) (see Table S1).

Table S2: Demographic variables. Mean (standard deviation) for age and intelligence level (IQ), number of males and females in each group created based on a Val-dominant model.

	Val carriers (N=30)	**Met/Met (N=13)**
Age	24.00 (2.23)	22.92 (2.06)
IQ	54.13 (3.28)	54.46 (2.18)
Gender (M/F)	13/17	8/5

Behavioural results

Analyses using a Met-dominant model

We conducted a repeated measure 2 (context) x 2 (item) ANOVA on median RTs for correct responses with group (VV vs. Met allele carriers) as an independent variable. First, we observed a main

effect of item [F(1,41) = 11.46; p = .001]. As expected, slower RTs were observed for RN than NN items. We did not observe any effect of context [F(1,41) = 0.02; p = .88] or group [F(1,41) = 0.29; p = .59]. There was no significant interaction between item and context [F(1,41) = 0.71; p = .41], between item and group [F(1,41) = 3.60; p = .06] or between context and group [F(1,41) = 0.02; p = .89].

For RTs, we conducted a repeated measure 2 (context) x 2 (item) ANOVA on item accuracy with group (VV vs. Met allele carriers) as an independent variable. Again, a significant effect of item [F(1,41) = 8.03; p < .007] was observed, with better performance for NN items than RN items. We did not observe any effect of context [F(1,41) = 2.19; p = .15] or group [F(1,41) = 0.32; p = .58]. There were no significant interactions between item and context [F(1,41) = 0.78; p = .38], between item and group [F(1,41) = 0.41; p = .53] or between context and group [F(1,41) = 0.05; p = .82].

Analyses using a Val-dominant model

We conducted a repeated measure 2 (context) x 2 (item) ANOVA on median RTs for correct responses with group (MM vs. Val allele carriers) as an independent variable. First, we observed a main effect of item [F(1,41) = 6.87; p = .01]. As expected, slower RTs were observed for RN than NN items. We did not observe any effect of context [F(1,41) = 0.13; p = .72] or group [F(1,41) = 0.20; p = .66]. There was no significant interaction between item and context [F(1,41) = 0.87; p = .36], between item and group [F(1,41) = 0.003; p = .95] or between context and group [F(1,41) = 0.20; p = .66].

For RTs, we conducted a repeated measure 2 (context) x 2 (item) ANOVA on item accuracy with group (MM vs. Val allele carriers) as an independent variable. Again, a significant effect of item [F(1,41) = 8.32; p < .007] was observed, with better performance for NN items than RN items. We did not observe any effect of context [F(1,41) = 1.42; p = .24] or group [F(1,41) = 0.50; p = .48]. There were no significant interactions between item and context [F(1,41) = 2.81; p = .10], between item and group [F(1,41) = 0.70; p = .41] or between context and group [F(1,41) = 0.19; p = .67].

fMRI results

Neural substrates of the interference effect for the whole task

Table S3
General interference effect – Comparisons by genotype and comparisons based on a Met-dominant model.

Hemisphere	Anatomical region	MNI coordinates			Cluster size	Z score	P value
		x	y	z			
Comparisons by genotype							
VM>MM							
R	Precuneus	20	–66	40	23	3.34	< .001
MM>VV; MM>VM; VV>VM; VM>VV; VV > MM Nil							
Comparisons based on Met-dominant model							
VV > VM & MM; VM & MM > VV Nil							

Note. Local maxima of brain regions showing more transient brain activity in RN than NN trials in the MI and MC contexts at a voxel *p* value < .001 uncorrected.

L/R = left or right; x, y, z: coordinates (mm) in the stereotactic space defined by the Montreal Neurological Institute (MNI).

Neural substrates of the interference effect in the reactive control condition

Table S4
Interference effect in reactive condition – All participants

Hemisphere	Anatomical region	MNI coordinates			Cluster size	Z score	P value
		x	y	z			
Activation Nil							
Deactivation							
	Posterior cingulate	12	–52	20	61	3.27	< .001
	Precuneus	10	–60	26	61	3.38	< .001
	Middle temporal gyrus	48	–64	26	12	3.48	< .001

Note. Local maxima of brain regions showing more transient brain activity in RN than NN trials during MC blocks at a voxel *p* value < .001 uncorrected.

L/R = left or right; x, y, z: coordinates (mm) in the stereotactic space defined by the Montreal Neurological Institute (MNI).

Table S5
Interference effect in reactive control condition using sex as a covariate – Comparisons by genotype and Comparisons based on a Met-dominant model.

Hemisphere	Anatomical region	MNI coordinates			Cluster size	Z score	P value
		x	y	z			
Comparisons by genotype							
VV>MM							
R	Anterior cingulate	2	10	-8	24	3.65	< .001
VM>MM							
R	Precentral gyrus	-42	-8	60	18	3.59	< .001
MM>VV; MM>VM; VV>VM; VM>VV Nil							
Comparisons based on Met-dominant model							
VV > VM & MM; VM & MM > VV Nil							

Note. Local maxima of brain regions showing more transient brain activity in RN than NN trials during MI blocks at a voxel *p* value < .001 uncorrected.

L/R = left or right; x, y, z: coordinates (mm) in the stereotactic space defined by the Montreal Neurological Institute (MNI).

Neural substrates of the interference effect in the proactive control condition

Table S6

Interference effect in proactive condition – All participants

Hemisphere	Anatomical region	MNI coordinates			Cluster size	Z score	P value
		x	y	z			
Activation							
	Middle frontal gyrus	26	44	–2	20	3.68	< .001
	Inferior parietal lobule	–50	–64	44	18	3.52	< .001
Deactivation Nil							

Note. Local maxima of brain regions showing more transient brain activity in RN than NN trials during MI blocks at a voxel *p* value < .001 uncorrected.

L/R = left or right; x, y, z: coordinates (mm) in the stereotactic space defined by the Montreal Neurological Institute (MNI).

Table S7

Interference effect in proactive control condition – Comparisons by genotype.

Hemisphere	Anatomical region	MNI coordinates			Cluster size	Z score	P value
		x	y	z			
VV>MM							
L	Superior frontal gyrus	–36	54	20	128	3.76	< .0001
R		34	56	22	80	3.48	< .001
R	Middle frontal gyrus	40	58	–6	24	3.69	< .001
R		46	54	2	24	3.22	< .001
L		–34	38	32	91	3.60	< .001
R		38	40	28	80	3.21	< .001
R		38	46	22	80	3.19	< .001
L		–30	10	50	13	3.36	< .001
R		38	22	52	37	3.32	< .001
R	Inferior frontal gyrus	42	32	4	484	4.05	< .0001
R		34	24	–8	484	3.56	< .0001
R		60	16	30	478	3.63	< .001
R		56	20	18	478	3.54	< .001
L	Medial frontal gyrus	–12	–14	54	1125	3.85	< .0001
R		10	–20	52	24	3.29	< .001
L	Precentral gyrus	–62	10	14	93	3.75	< .0001
R		62	6	14	52	3.71	< .001
R		58	0	28	487	3.49	< .001
L		–58	–2	24	94	3.38	< .001
L	Postcentral gyrus	–66	–8	18	94	3.51	< .001
R		44	–24	50	34	3.42	< .001
L		–46	–18	34	58	3.40	< .001
L	Cingulate gyrus	–16	6	42	76	3.91	< .0001
L		–10	–2	30	14	3.40	< .001
L		–8	–30	32	17	3.28	< .001
L	Insula	–38	–12	8	577	3.88	< .0001
L		–42	–20	2	577	3.87	< .0001
R	Inferior parietal lobule	56	–38	34	31	3.39	< .001
L	Thalamus	–18	–26	0	57	3.47	< .001
L		–10	–4	2	57	3.30	< .001
R	Angular gyrus	38	–64	36	19	3.27	< .001
R	Superior temporal gyrus	52	–10	–8	227	4.03	< .0001
R		48	–36	10	223	4.02	< .0001
L		–50	–26	6	577	3.68	< .0001
R	Transverse temporal gyrus	42	–26	10	223	3.81	< .0001
L		–34	–36	12	67	3.44	< .001

L	Fusiform gyrus	–56	–8	–28	173	3.77	< .0001
R	Precuneus	20	–6	36	13	3.17	< .001
R	Caudate	6	16	6	24	3.36	< .001
R	Paracentral lobule	6	–38	64	1125	3.93	< .0001
R	Lentiform nucleus	20	12	–4	1125	3.96	< .0001
VV>VM							
L	Superior frontal gyrus	–30	54	28	20	3.35	< .001
R	Inferior frontal gyrus	62	14	28	25	3.37	< .001
R		46	38	16	15	3.25	< .001
R	Medial frontal gyrus	16	8	48	29	3.63	< .001
L		–14	–14	54	33	3.56	< .001
R		10	–18	58	34	3.36	< .001
L	Precentral gyrus	–62	8	14	23	3.43	< .001
L		–58	–2	30	29	3.23	< .001
R	Insula	40	–2	14	11	3.27	< .001
VM>MM							
R	Inferior frontal gyrus	38	32	8	10	3.29	< .001
R	Superior temporal gyrus	46	–38	6	27	3.58	< .001
L	Middle temporal gyrus	–46	–62	10	20	3.69	< .001
R		42	10	–36	12	3.30	< .001
R	Fusiform gyrus	26	–84	–22	28	3.78	< .0001
L		–30	–34	–20	11	3.37	< .001
R	Culmen	18	–38	–22	24	3.49	< .001
MM>VV; MM>VM; VM>VV Nil							

Note. Local maxima of brain regions showing more transient brain activity in RN than NN trials during MI blocks at a voxel *p* value < .001 uncorrected.

L/R = left or right; x, y, z: coordinates (mm) in the stereotactic space defined by the Montreal Neurological Institute (MNI).

Table S8

Interference effect in proactive control condition – Comparisons based on a Met-dominant model.

Hemisphere	Anatomical region	MNI coordinates			Cluster size	Z score	P value
		x	y	z			
VV > VM & MM							
L	Superior frontal gyrus	–30	54	28	173	3.70	< .001
L	Middle frontal gyrus	–36	36	30	173	3.43	< .001
R		38	24	50	51	3.45	< .001
L		–30	10	46	14	3.28	< .001
L	Inferior frontal gyrus	–58	6	32	315	3.37	< .001
R		62	14	28	236	3.72	< .001
R		54	10	28	236	3.50	< .001
R		52	20	16	236	3.35	< .001
R		44	34	6	194	3.64	< .001
R		44	36	14	194	3.62	< .001
R		58	34	4	194	3.42	< .001
L	Medial frontal gyrus	–14	–14	54	254	3.92	< .0001
L		–6	–6	58	254	3.22	< .001
R		8	–20	54	106	3.58	< .001
R		16	8	48	28	3.44	< .001
L	Precentral gyrus	–30	–32	60	254	3.57	< .001
L		–62	10	14	315	3.81	< .0001
L		–58	–2	28	315	3.53	< .001
R		14	–22	70	106	3.19	< .001
R		62	6	14	11	3.28	< .001
L	Cingulate gyrus	–14	6	42	51	3.58	< .001
L		–10	–26	30	10	3.25	< .001
R	Insula	40	–4	12	29	3.28	< .001
L		–38	–12	12	31	3.25	< .001
R	Angular gyrus	38	–60	30	13	3.40	< .001
L	Superior temporal gyrus	–54	–10	–2	34	3.33	< .001
L	Middle temporal gyrus	–54	–4	–8	34	3.12	< .001
L	Supramarginal gyrus	–48	–48	38	11	3.20	< .001

L	Fusiform gyrus	–56	–8	–28	33	3.43	< .001
R	Caudate	8	18	6	13	3.23	< .001
L	Paracentral lobule	–18	–42	52	27	3.38	< .001
L		–12	–36	60	13	3.23	< .001
R	Lentiform nucleus	20	12	–2	106	3.60	< .001
VM & MM > VV							
Nil							

Note. Local maxima of brain regions showing more transient brain activity in RN than NN trials during MI blocks at a voxel *p* value < .001 uncorrected.

L/R = left or right; x, y, z: coordinates (mm) in the stereotactic space defined by the Montreal Neurological Institute (MNI).

Table S9

Interference Effect in Proactive Control Condition using sex as covariate – Common Features between Comparisons by Genotype and Comparisons using a Met-dominant model.

Hemisphere	Anatomical region	MNI coordinates			BA	Cluster size	Z score	P value
		x	y	z				
Comparisons by genotype								
VV > MM								
L	Superior frontal gyrus	–34	54	24	10	326	4.15	< .0001
R	Medial frontal gyrus	18	–36	66	6	2294	4.22	< .0001
L		–6	–10	52	6	2294	4.10	< .0001
R	Inferior frontal gyrus	60	16	30	9	161	3.63	< .0001
		42	32	4	46	344	3.90	< .0001
L	Precentral gyrus	–62	10	14	44	1924	4.02	< .0001
		–56	–6	-28	6	94	4.01	< .001
VV > VM								
L	Superior frontal gyrus	–30	54	28	10	7	3.24	< .001
R	Medial frontal gyrus	10	–18	58	6	19	3.27	< .001
L		–14	–14	54	6	22	3.46	< .001
R	Inferior frontal gyrus	62	14	28	9	13	3.27	< .001
		46	38	16	46	5	3.17	< .001
L	Precentral gyrus	–62	8	14	44	11	3.33	< .001
		–58	–2	30	6	6	3.15	< .001
Comparisons by allele								
VV > VM & MM								
L	Superior frontal gyrus	–30	54	28	10	200	3.81	< 0.001
R	Medial frontal gyrus	8	–18	58	6	138	3.60	< .001
L		–14	–14	54	6	332	3.93	< .0001

R	Inferior frontal gyrus	62	14	28	9	295	3.69	< .001
		44	36	14	46	248	3.72	< .0001
L	Precentral gyrus	–62	10	14	44	437	3.91	< .0001
		–58	–4	26	6	437	3.65	< .001

Note. Local maxima of brain regions showing more transient brain activity for the interference effect (recent negative vs. non-recent negative items) in VV homozygous individuals during MI blocks at a voxel p value < .001 uncorrected.

L/R = left or right; x, y, z: coordinates (mm) in the stereotactic space defined by the Montreal Neurological Institute (MNI); BA = Brodmann Area.

Time course of the interference effect in the proactive control condition

For the right IFG (62 14 28), the 4-way (phase) ANOVA on FIR_II with group as independent variable showed no effect of phase [$F(3,123) = 1.19$; $p = .32$] or group[$F(1,41) = 0.36$; $p = .55$], and no interaction between phase and group [$F(3,123) = 1.27$; $p = .29$].

For the right IFG (44 36 14), the 4-way (phase) ANOVA on FIR_II with group as independent variable showed no effect of phase [$F(3,123) = 0.77$; $p = .51$] or group[$F(1,41) = 0.08$; $p = .78$], and no interaction between phase and group [$F(3,123) = 0.52$; $p = .67$].

For the right MedFG (8 –20 54), the 4-way (phase) ANOVA on FIR_II with group as independent variable showed no effect of phase [$F(3,123) = 1.11$; $p = .35$] or interaction between phase and group [$F(3,123) = 2.17$; $p = .10$]. Nevertheless, a main effect of group [$F(1,41) = 6.53$; $p = .01$], characterized by a higher FIR_II in Met allele carriers, was observed.

For the left MedFG (–14 –14 54), the 4-way (phase) ANOVA on FIR_II with group as independent variable showed no effect of phase [$F(3,123) = 0.32$; $p = .81$] or group [$F(1,41) = 0.12$; $p = .73$], and no interaction between phase and group [$F(3,123) = 0.27$; $p = .85$].

For the left PcG (–62 10 14), the 4-way (phase) ANOVA on FIR_II with group as independent variable showed no effect of phase [$F(3,123) = 1.14$; $p = .34$] or group [$F(1,41) = 1.54$; $p = .22$], and no interaction between phase and group [$F(3,123) = 0.18$; $p = .91$].