Influence of COMT Genotype on Antero-Posterior Cortical Functional Connectivity Underlying Interference Resolution

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Abstract

Genetic variability related to the catechol-O-methyltransferase (COMT) gene (Val^{158}Met) has received increasing attention as a possible modulator of executive functioning and its neural correlates. However, this attention has generally centred on the prefrontal cortices because of the well-known direct impact of COMT enzyme on these cerebral regions. In this study, we were interested in the modulating effect of COMT genotype on anterior and posterior brain areas underlying interference resolution during a Stroop task. More specifically, we were interested in the functional connectivity between the right inferior frontal operculum (IFop), an area frequently associated with inhibitory efficiency, and posterior brain regions involved in reading/naming processes (the two main non-executive determinants of the Stroop effect). The Stroop task was administered during fMRI scanning to three groups of 15 young adults divided according to their COMT Val^{158}Met genotype [Val/Val (VV), Val/Met (VM) and Met/Met (MM)]. Results indicate greater activity in the right IFop and the left middle temporal gyrus (MTG) in homozygous VV individuals than in Met allele carriers. In addition, the VV group exhibited stronger positive functional connectivity between these two brain regions and stronger negative connectivity between the right IFop and left lingual gyrus. These results confirm the impact of COMT genotype on frontal function. They also strongly suggest that differences in frontal activity influence posterior brain regions related to a non-executive component of the task. Especially, changes in functional connectivity between anterior and posterior brain areas might correspond to compensatory processes for performing the task efficiently when the available dopamine level is low.

Keywords: Inhibition - fMRI - COMT gene - Stroop task

Introduction

Efficient inhibitory abilities are necessary to maintain an adequate level of adjustment to environmental demands. Inhibition is classically considered to consist of a set of processes that allow one to suppress the production of a predominant but inappropriate response in order to promote a more adapted one (e.g., Nigg, 2000). The neural correlates of inhibition have been widely studied in the past two decades through perceptual, motor and semantic paradigms. These studies showed the involvement of an extensive brain network including the cingulate, prefrontal, parietal and temporal areas (Bench et al., 1993; Bush et al., 1998; Chee et al., 2000; Collette et al., 2001; Garavan et al., 1999; Larrue et al., 1994; Pardo et al., 1990; Taylor et al., 1997).

Among these brain areas, the anterior cingulate cortex (ACC) plays a central role in the detection and resolution of conflicting situations (Carter et al., 1998; Kerns et al., 2004). More specifically, in the context of the conflict monitoring hypothesis proposed by Botvinick et al. (2001), once a conflict is detected by the ACC, this area will recruit the dorsolateral prefrontal cortices (DLPFC) to adjust behaviour to the conflicting situation. This adjustment will be made by biasing information processing in posterior brain areas towards the cognitive processes that are most relevant to task goal and context. Consequently, the DLPFC is considered to be the brain area specifically involved in implementing strategic adjustments in cognitive control when the ACC detects conflicting situations. Moreover, the activity in the DLPFC in response to conflicting situations is often associated with increased activity in the right inferior frontal gyrus (IFG) (Garavan et al., 2002; Garavan et al., 1999; Konishi et al., 1999; Rubia et al., 2003) and especially the right pars triangularis of the IFG (for a review, see Aron et al., 2004, 2014).

A series of neuroimaging data support the conflict monitoring theory proposed by Botvinick et al. (2001; Botvinick et al., 2004), which argues that, following conflict detection, the ACC recruits the DLPFC, which in turn inhibits a response by biasing information processing in posterior brain areas.

Kerns et al. (2004) showed that the activity in the ACC for conflicting trials predicted subsequent prefrontal cortex (PFC) activity and adjustments in behaviour. Egner and Hirsh (2005) showed not only that response inhibition in situations of conflict adaptation was associated with increased activity in the PFC, but also that activity in this area was accompanied by increased functional integration with parietal and temporal gyri. Polk et al. (2008) observed that the presentation of interfering items during a Stroop task (Stroop, 1935), which requires subjects to inhibit the overlearned reading process in favour of a colour naming process, generated increased activity in brain areas previously associated with colour processing (bilateral lingual gyrus), while brain activity in word processing areas (left fusiform gyrus) tended to decrease. As a whole, these studies demonstrated that inhibition of an irrelevant response or process involves the dynamic interplay of several anterior and posterior brain areas.

Several lines of evidence suggest that the neurotransmitter dopamine (DA) plays an important role in cognitive functions associated with prefrontal activity, such as executive processes (for a review, see Witte & Flöel, 2012). Catechol-O-methyltransferase (COMT) is the major enzyme involved in the metabolic degradation of released DA, accounting for more than 60% of DA degradation in the frontal cortex (Karoum et al., 1994). The human *COMT* gene, located on the long arm of chromosome 22q11 (Mannisto & Kaakkola, 1999), contains a functional polymorphism in codon 158 ($Val^{158}Met$), which affects the enzyme's activity (Chen et al., 2004; Lachman et al., 1996). A transition of guanine to adenine results in a valine-to-methionine substitution; consequently, there are three different COMT genotypes (GG, GA, AA), corresponding respectively to Val^{158}/Val^{158}, Val^{158}/ Met^{158}, Met^{158}/ Met^{158}. Each genotype 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 (Chen et al., 2004; Lotta et al., 1995). As DA plays an important role in human cognition (Kimberg et al., 1997; Mehta et al., 2000), COMT $Val^{158}Met$ polymorphism (rs4680) can be considered as a useful tool for

investigating the modulating effect of DA on the brain areas associated with the conflict resolution processes.

Few studies so far have explored the influence of COMT polymorphism on the neural substrates of conflict/interference resolution processes, and most of them were interested in motor inhibition. For example, Congdon et al. (2009) used a stop-signal task and showed higher activity in the right inferior frontal operculum (IFop) during stop trials in carriers of the Met allele. Because all groups' behavioural performance was similar and several functional magnetic resonance imaging (fMRI) studies of the stop-signal task have demonstrated that enhanced responses relate to better inhibitory control in that task (Aron & Poldrack, 2006; Li et al., 2006), the authors concluded that this result reflected better inhibitory control in Met allele carriers. Similarly, Stokes et al. (2011) found more activity in the right posterior cingulate gyrus in Met carriers for No-Go trials than for Go trials. However, no significant association was found between PFC activation and COMT genotype. In addition, the authors did not detect an effect of COMT genotype on functional connectivity between the posterior cingulate and anterior brain areas. Finally, Ettinger et al. (2008) reported a lower BOLD response in the ventromedial and dorsomedial prefrontal cortex in Val carriers during an antisaccade task, again indicating more activity for Met carriers when oculomotor inhibition is required. Together, these results support the hypothesis that individuals homozygous for the Val allele are characterized by a less-efficient physiological response in cingulate and prefrontal areas during motor inhibition processes. Nevertheless, it must be emphasized that fMRI effects in these studies were observed in the absence of any effect of genotype on behavioural efficiency. Interestingly, such an absence of effect was also observed when the procedure used was supposed to emphasize between-group differences. Indeed, Plewnia et al. (2013) observed no impact of COMT genotype on the accuracy of responses in a Go/No-Go task during transcranial direct current stimulation applied to the left DLPFC.

The influence of COMT polymorphism on perceptual inhibition was addressed by Blasi et al. (2005), who used a flanker task with three levels of attentional control. For the medium and high levels of attentional control, they showed a main effect of COMT genotype in the dorsal cingulate, with higher activity for VV individuals, followed by VM and then by MM. As MM individuals were also more accurate at the high attentional control level, this pattern of brain activity was interpreted as suggesting less efficient cortical processing of stimuli and a less efficient allocation of attentional resources in individuals who are homozygous for the Val allele. Finally, our group explored the effect of COMT polymorphism on cognitive control using a Stroop inhibition task (Jaspar et al., 2014). According to the Dual Mechanism of Control (DMC) theory (Braver et al., 2007), proactive control mechanisms, which are a sustained form of control, specialize in interference prevention and anticipation, whereas reactive control mechanisms are dedicated to detecting and resolving interference when it occurs. Consequently, one strategy is favoured over the other depending on whether there is a high or low occurrence of interfering events. In agreement with the DMC model, we observed that the neural substrates of proactive control are modulated by the level of DA available, with sustained increased activity in the ACC and decreased activity in the middle frontal gyrus in carriers of the Met allele. However, contrary to the model's predictions, we also observed an effect of DA in the reactive control condition, with individuals who are homozygous for the Val allele presenting consistently higher transient activity in the right IFop when interfering items were presented.

Aim of the Study and A Priori Hypothesis

We had previously observed (Jaspar et al., 2014) that, in a Stroop task, Val individuals exhibit greater transient activity in the right IFop when they must deal with the relatively infrequent presentation of interfering items (i.e., in the task condition requiring them to implement reactive control). This increased activity can be interpreted as reflecting less efficient cortical processing of the presented information in frontal areas (for a similar interpretation, see Blasi et al., 2005). As previous

studies had shown that performance on the Stroop task is associated with a large fronto-temporo-parietal network (e.g., Laird et al., 2005; Nee et al., 2007), the aim of the present study is to complement our previous analyses and determine whether the COMT polymorphism's effect on inhibition abilities can also be expressed on posterior brain areas and/or modulate functional connectivity between anterior and posterior brain areas.

With that objective, the data set acquired to test the dopaminergic hypothesis of the DMC account (Braver et al., 2007) in our previous study (Jaspar et al., 2014) was reanalysed with a focus on the reactive control condition only. As Stroop tasks used in past studies (Banich et al., 2000; Milham et al., 2002; Ruff et al., 2001) were generally composed of around 50% interfering events, we considered the reactive condition (composed of 17% interfering items) to be more appropriate than the proactive one for exploring the neural substrates of the interference effect. Moreover, our reactive task condition is very similar to some task designs (e.g., Grandjean et al., 2012; Leung, et al., 2000) showing the classical fronto-parieto-temporal pattern of brain activity following presentation of interfering Stroop items. In contrast to our previous study, we extended the fMRI analyses of COMT influence on the interference effect to the whole brain. We also assessed the presence of a differential effect of COMT polymorphism on functional connectivity between frontal and posterior brain areas.

Our predictions were the following. We expected a modulating effect of COMT polymorphism on posterior brain regions in addition to the previously reported effect in the right IFop. Indeed, in the dynamic interplay between anterior and posterior regions during performance of a Stroop task (see Botvinick et al., 2001, 2004), changes in prefrontal activity depending on the presence of Val or Met alleles should impact activity in the parietal and temporal areas also involved in the processing of interfering items. More specifically, we expected to observe an influence of COMT genotype in areas associated with reading (occipito-temporal junction, basal temporal area, middle temporal and inferior frontal gyri [Jobard et al., 2003]) and colour processing (bilateral lingual and fusiform gyri [Polk et al.,

2008]). Psychophysiological interactions were also computed to test the hypothesis that the functional connectivity of the right IFop and the rest of the brain differs for interfering items depending on COMT polymorphism. In fact, we expected that individuals who were homozygous for the Val allele would present: (1) a smaller positive association between the right IFop and the brain areas that facilitate interference resolution (the ACC, associated with conflict detection [Carter et al., 1998]; the bilateral DLPFC, the right inferior parietal lobule and the left precuneus, associated with response inhibition during a Stroop task [Nee et al., 2007]; and the bilateral lingual and fusiform gyri, associated with colour detection [Polk et al., 2008]); (2) a stronger positive association between the right IFop and brain regions that impede interference resolution (the left lateralized cerebral network associated with word reading [occipito-temporal junction, basal temporal area, middle temporal and inferior frontal gyri; Jobard et al., 2003]).

Methods

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.

Participants

One hundred and six Caucasian right-handed native French-speaking young adults, aged from 18 to 30, with no diagnosed psychological or neurological disorders, were recruited from the university community and paid for their participation. All had normal colour vision. Each participant was also screened for any physical or medical condition that could prevent an MRI session. Through a DNA screening, our sample was separated into three groups according to their COMT genotype: 30 homozygous Val/Val (VV), 27 homozygous Met/Met (MM) and 49 heterozygous Val/Met (VM). Fifteen subjects were selected from each group in order to match them for gender [$F(2) = 0.60$, $p = 0.55$], age

[$F(2) = 0.94$, $p = 0.40$] and fluid intelligence level [$F(2) = 1.96$, $p = 0.15$] (see Table S1 in supplemental materials). Fluid intelligence level was assessed using Raven's advanced progressive matrices test (Raven, Court, & Raven, 1983).

Genotyping

Genomic DNA was extracted from blood samples using a MagNA Pure LC Instrument (Roche Applied Science). The DNA sequence of interest was amplified by 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 samples then underwent the pyrosequencing reaction (Pyromark Q96 Vacuum Workstation, PSQ 96MA, Pyromark Gold Q96 Reagents, Qiagen). The sequences of primers that were used are available upon request.

Materials and Procedure

A modified form of the Stroop task (Grandjean et al., 2012) with four words presented on a white background (the French equivalents of *Red, Blue, Black,* and *Green*) was used for this experiment and is described in full details in Jaspar et al. (2014; see also Supplementary Figure 1). Proportion congruency was manipulated using three different contexts of 12 items each): the mostly incongruent context (MI), the mostly congruent context (MC), and the mostly neutral context (MN). Each MI block was composed of 8 incongruent items (II; e.g., the word *red* written in blue), 2 congruent items (CI; e.g., the word *blue* in blue), and 2 neutral items (NI), which were nonverbal stimuli (i.e., strings of five per cent signs %%%%%) presented in one of the four colour possibilities. For the MC context, the proportions of congruent and incongruent items were reversed. Finally, 8 neutral, 2 congruent, and 2 incongruent items were presented during the MN context. Importantly, the first four items in each block

were representative of the current task context (e.g., four incongruent trials at the beginning of each MI context) and were intended to induce the use of proactive or reactive control processes. The presentation order of the different blocks was pseudo-randomized, with the use of three different presentation orders. Each of the three congruency conditions of 12 items (MI, MC, and MN contexts) was presented 15 times, for a total of 45 blocks and 540 items.

The participants were instructed that their task would be to select the colour in which each item was printed by pressing the corresponding key on a keyboard. They were told that the items would be presented briefly and that they would have to respond as fast and accurately as possible. Colour words were presented on a screen that the participants viewed through a mirror located on the scanner's head coil. Each trial consisted of the presentation of a word in the centre of the screen, with four response possibilities at the bottom of the screen (corresponding to the four colour possibilities, always in the same order). Each item was presented until the participant responded (with a maximum presentation time of 2000 ms). If the participant responded before the deadline, a white screen was presented for the remaining period. If no response was provided, a white screen appeared after 2000 ms and an inter-stimulus interval of 500 ms occurred before the next item. A fixation cross was presented in the centre of the screen for 5000 ms after every two or three contexts to provide breaks during the experiment.

Prior to the fMRI session, participants performed a practice session outside the scanner in which 40 items were presented to be sure that they understood the task instructions. In the fMRI scanner, four more examples were presented just before the test phase began. After the session, participants received a debriefing that explained the main objective of the experiment.

Behavioural Data Analysis

All behavioural data analyses were conducted with a statistical level set at $p < .05$. Repeated measures ANOVAs were run on the median reaction times (RTs) and accuracy data (proportion of correct responses), with task context (MC, MI, and MN) and item type (II, CI, and NI) as repeated

measures factors. Finally, planned comparisons were performed, also with a p <.05, using univariate tests of significance.

fMRI Acquisition and Analyses

Functional MRI time series were acquired on a 3T head-only scanner (Magnetom Allegra, Siemens Medical Solutions, Erlangen, Germany) operated with the standard transmit-receive quadrature head coil. Structural images were obtained using a high-resolution T1-weighted sequence (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-planar imaging sequence using axial slice orientation and covering the whole brain (32 slices, FoV = 220 x 220 mm^2, voxel size 3.4 x 3.4 x 3 mm^3, 30% interslice gap, matrix size 64 x 64 x 32, TR = 2130 ms, TE = 40 ms, FA = 90°). In each session, between 570 and 650 functional volumes were obtained. The first three volumes were discarded to account for T1 saturation. Stimuli were displayed on a screen positioned at the rear of the scanner, which the participant could see comfortably through a mirror mounted on the standard head coil.

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). 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 in 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 10-mm full-width at half-maximum (FWHM) Gaussian kernel.

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 three contexts (MI, MC, or MN) and the type of item (II, CI, or NI). These 9 regressors were modelled as event-related responses. Event durations corresponded to the presentation of the item until the subject's response, with a maximum duration of 2 s. Incorrect trials and non-responses were also modelled as separate regressors. The design matrix also included the realignment parameters to account for any residual movement-related effect. In addition, the first four items for each context were modelled separately in the design matrix. The rationale for excluding those items was that they did not fully reflect the cognitive control strategy postulated for the context in question (i.e., in the MI context, the first items served to establish the subsequent proactive control strategy by creating expectations associated with that context, and similarly in the MC context, the first items created a low expectation of incongruent trials). A high pass filter was implemented using a cut-off period of 256 s in order to remove the low-frequency drifts from the time series. Linear contrasts assessed the simple main effect of each trial type. The resulting set of voxel values constituted a map of *t* statistics, SPM[T]. The corresponding contrast images were entered into a second-level analysis, corresponding to a random-effect model.

At the second level (random-effect analysis), a 3 (context) x 3 (item type) whole-brain voxel-wise repeated measures ANOVA was performed, which allowed us to examine the brain regions related to the comparisons of interest: (1) the general interference effect; and (2) the interference effect in the MC context (involving reactive control). First, these individual contrast images were used to analyse neural activity common to the three genotype groups. These analyses were conducted using a correction for multiple comparisons at the voxel level with a conservative family-wise error (FWE) threshold of $p < .05$ corrected. Second, we focused on genotype-related differences in the neural correlates of interfering events in the whole task but also when reactive control processes were specifically implemented. T-test comparisons between genotypes were performed at a p value < .001 uncorrected. Only the analyses assessing between-group comparisons of the neural substrates of the interference effect are detailed in

the main text. The extent threshold was set to more than 5 contiguous voxels. These analyses were first performed by comparing each genotype to the two others separately and next by grouping together participants carrying at least one Val or Met allele, respectively (VV and VM vs. MM, and VV vs. VM and MM). We will present and consider as relevant for the discussion only brain areas that are consistently found to be significant across these two analyses. The results of the following analyses are not reported in this paper but are available in our previous work (Jaspar et al., 2014): general interference effect common to the three groups across the MC, MI and MN contexts; interference effects common to the three groups and specific to the MC context.

To assess the hypothesis that the IFop, involved in interference resolution, interacts differently with the ACC and posterior brain areas between our groups, we conducted psychophysiological interaction (PPI) analyses. The logic underlying the choice of the right IFop as region of interest (ROI) for these analyses was that we had already shown that COMT genotype differently affects its involvement in response inhibition in conditions of reactive control (the MC context; Jaspar et al., 2014). The difference in cerebral activity between interfering and neutral items for the selected ROI (right IFop: x y z = 54 12 –2) in the MC context was extracted using a spherical 10-mm radius for each volunteer. A general linear model was used to perform PPI analyses. At the first level of the analyses (fixed effect), three regressors were created (without taking account of realignment parameters). The first regressor represented the interference effect (II – NI items in the MC context). The second one was the activity in the seed area. The third regressor represented the interaction of interest between the first (psychological) and the second (physiological) regressors. The contrast images obtained allowed us to determine, in each subject, the brain areas interacting significantly with the right IFop in respect of the psychological regressor. The contrast images were used at the second level (random-effect analysis) for between-group comparisons. Again, these analyses were performed first by comparing each genotype to the other two separately and then by grouping together participants carrying at least one Val or Met

allele, respectively. All consistent PPI results for our two analysis methods are presented with a threshold of $p < .001$, uncorrected. The extent threshold was set to 10 contiguous voxels. As performing PPI analyses with the input from a single ROI (here, the right IFop) cannot provide definite evidence of effective connectivity (Friston et al., 1997), the results obtained will be discussed in terms of functional connectivity (a correlation of activity in different regions).

Some previous studies reported a gender influence on behavioural Stroop performance (e.g. von Kluge, 1992) and also the presence of sexually-dimorphic effects of COMT on brain activation during inhibition (White et al., 2014). To exclude from our interpretations a potential sex influence, we also conducted our behavioral and fMRI analyses adding sex as a covariate. Anticipating on the next section, consideration of sex did not modify the results.

Results

Behavioural Results

We conducted a repeated 3 (context) x 3 (item) analysis of variance (ANOVA) on median RTs for correct responses, with group as an independent variable. Significant item [$F(2,84) = 207.73$; $p < .0001$] and context [$F(2,84) = 20.99$; $p < .0001$] effects were observed, but no significant group effect [$F(2,42) = 0.65$; $p = .53$]. Planned comparisons showed that the item effect is characterized by slower RTs for interfering than for neutral items [$F(1,42) = 200.70$; $p < .0001$]. This interference effect is observed in MI [$F(1,42) = 232.37$; $p < .0001$], MC [$F(1,42) = 102.23$; $p < .0001$] and MN [$F(1,42) = 160.56$; $p < .0001$] contexts.

As with RT, a 3 (context) x 3 (item) ANOVA on item accuracy, with group as an independent variable, was conducted. The pattern of results in terms of item and context effects is the same as for RT. Planned comparisons showed that the item effect is characterized by less accurate responses for interfering than neutral [$F(1,42) = 98.29$; $p < .0001$] items. Again, this interference effect is observed in MI [$F(1,42) = 60.42$; $p < .0001$], MC [$F(1,42) = 19.18$; $p < .0001$] and MN [$F(1,42) = 36.93$; $p < .0001$]

contexts. With regard to genotype, no significant group effect was found for item accuracy [$F(1,42) = 1.51$; $p = .23$]. However, a significant item x group interaction [$F(4,84) = 2.77$; $p = .03$] was observed. Indeed, significant differences in performance for the interfering items by comparison to neutral items (II – NI) are observed in the MM group, as compared to the VM [$F(1,42) = 4.85$; $p = .03$] and VV [$F(1,42) = 6.37$; $p = .02$] groups, with the MM group performing better. Interestingly, the same pattern of results is also observed specifically in the MC context, with better performance by the MM than the VM [$F(1,42) = 5.90$; $p = .02$] and VV groups [$F(1,42) = 6.92$; $p = .01$] (see figure S2 in supplemental materials).

Behavioural results associated with the MC context and requiring reactive control (the focus of the present report) can be summarized as follows. A significant interference effect was observed for RTs and accuracy. This effect is of similar amplitude in all three groups for RTs, while the MM group performed better in terms of accuracy. These effects were not modified when sex was used as a covariate in the analyses.

fMRI Results

As indicated in the methods section, fMRI analyses were first performed by comparing each genotype group to the other two separately and then by grouping together participants carrying at least one Val or Met allele, respectively. In the text and the results tables, we will report only on the brain areas that were initially found in the first analysis (comparison of each genotype to the two others) and confirmed by the second one (comparisons of allelic groups). A complete description of the results obtained by these two approaches can be found in the supplemental data (see Tables S2 to S7).

The neural substrates of the interference effect for the task as a whole. First of all, the general interference effect (i.e., II vs. NI) in the whole sample of participants revealed a large map of activation corresponding to the extensive fronto-parieto-temporal network typically associated with interference resolution in the Stroop task (see Jaspar et al., 2014).

Interestingly, when the transient pattern of cerebral activity for interfering items (compared to neutral ones) in the contexts that most induce the reading process (the MI and MC contexts, composed of 75% interfering or facilitator items) was compared between the VV, VM and MM participants, we observed greater brain activity in the left superior temporal gyrus (STG) in VV and VM groups than in the MM group. This result was confirmed in the analysis conducted by grouping the Val allele carriers together and comparing them to the homozygous MM group (see Table 1). These effects were not modified when sex was used as a covariate in the analyses.

[INSERT TABLE 1]

The neural substrates of the interference effect in the reactive control condition. The interference effect (i.e., II vs. NI) in the whole sample of participants during the MC task context (i.e., when only 17% of interfering items were presented) again revealed a network of activation in fronto-parietal areas and increased activity in the insula and the cerebellum (Jaspar et al., 2014).

The transient activity in the whole brain for interfering items (compared to neutral ones) during the MC context was compared for our three groups of volunteers (VV, VM and MM) and by grouping together participants carrying at least one Val or Met allele. Interestingly, we again observed increased cerebral activity in the left STG (see Figure 1a) in Val allele carriers by comparison to homozygous MM individuals (VV > MM; VM > MM; VV and VM > MM). Moreover, the left middle temporal gyrus (MTG), the right IFop and the left precentral gyrus (PcG) (see Figure 1b) appeared to be less activated in Met allele carriers (VV > VM; VV > MM; VV > VM and MM) (see Table 2). These effects were not modified when sex was used as a covariate in the analyses.

[INSERT TABLE 2 & FIGURE 1]

Psychophysiological interactions in the reactive control condition. As the right frontal operculum has frequently been associated with inhibitory processes and was more activated by VV

individuals when reactive control was required (Jaspar et al., 2014), we compared the functional connectivity between that area and the rest of the brain in our three groups of participants.

We observed that individuals carrying at least one Val allele have consistently greater positive functional connectivity of the right IFop with the right cingulate gyrus and right STG than homozygous Met individuals (VV > MM, VM > MM, VV and VM > MM). We also observed that activity in the IFop of homozygous Val carriers was more associated with the right superior frontal gyrus (SFG), left mid-cingulate gyrus, left MTG extending to the STG and left lingual gyrus than in homozygous and heterozygous carriers of the Met allele (VV > MM, VV > VM, VV > VM and MM) (see Table 3). Note that the MTG observed here overlaps the left MTG area reported for the interference effect in the reactive condition (see Table 2). Interestingly, the right IFop is positively associated with the first three regions but negatively with the lingual gyrus (see Figure 2). Finally, no increased functional connectivity was observed between the right IFop and the rest of the brain for carriers of the Met allele by comparison to homozygous and heterozygous Val participants (MM > VV, MM > VM, VM > VV, MM > VV and VM, MM and VM > VV). Similar results were observed when sex was used as a covariate in the PPI analyses (see Table S8).

[INSERT TABLE 3 & FIGURE 2]

Discussion

The objective of this study was to determine if the COMT polymorphism's effect on inhibition previously observed in frontal areas (Blasi et al., 2005; Congdon et al., 2009; Jaspar et al., 2014) is also expressed in posterior brain areas and whether this polymorphism modulates the functional connectivity between anterior and posterior brain areas.

From a behavioural point of view, it appeared that VV and VM participants were more sensitive to interference than MM participants. Indeed, these volunteers were less efficient at processing interfering events (compared to neutral ones), as revealed in their response accuracy. It is noteworthy

that the decreased accuracy for incongruent events in the Val allele carrier groups was observed even though the groups of participants were matched for age, IQ and other demographic factors. In parallel to these observations, we also showed that the same individuals (VV and VM) presented greater brain activity in the left STG when they had to resolve interference. We also reproduced our previous data showing an increase in activity in the right IFop in VV group by comparison to the two other groups when interfering items were presented. Additionally, we observed that VV individuals presented higher brain activity in the left PcG, a region regularly involved in Stroop inhibitory tasks (Laird et al., 2005), and the MTG. Now, with regard to functional connectivity analyses, we showed that activity in the right IFop is more positively linked to activity in the right cingulate and superior temporal gyri in individuals carrying at least one Val allele (compared to homozygous Met individuals). Moreover, brain activity in the right IFop in homozygous Val carriers is more positively associated than in Met allele carriers with the right SFG, the left mid-cingulate and middle temporal gyri, but more negatively with the lingual gyrus. Considering that the right IFop presented a higher level of activity in homozygous VV participants only (compared to the other two groups), we will focus our discussion of PPI differences on the comparison of VV individuals with Met allele carriers. Finally, as some studies reported evidence of sexually-dimorphic effects of COMT on behavioural performance (Soeiro-De-Souza et al., 2013) and brain activity (White et al., 2014) during executive tasks, we replicated our analyses using sex as covariate. These last analyses highlighted that genotypic differences in behaviour and brain activity observed here are independent of any sex effect.

What Is the Role of Posterior Brain Regions Observed to Be Differently Modulated by COMT Polymorphisms during the Stroop Task?

Two posterior areas appeared differently affected between *COMT* allelic groups during the Stroop task. First, participants with at least one Val allele exhibited less deactivation in the left STG for interfering than for neutral items. Second, the homozygous Val group presented greater activity in the

left MTG for interfering than for neutral stimuli. As it is also commonly accepted that language abilities, and specifically reading processes, are subserved by temporal areas (Jobard et al., 2003), the involvement of these two regions could plausibly be related to the reading induced by the Stroop task. More specifically, based on the dual-route model of reading (Coltheart et al., 1993), the left MTG and STG may be related to two different aspects of word reading processes. Indeed, this model postulates that, after preliminary visual analyses, words can be read by two different routes. The direct one, the lexico-semantic route, allows a direct association between the visual form of the word and its meaning. The indirect, or grapho-phonological, route involves a grapheme-to-phoneme conversion to transform the word to its auditory form and access its meaning. A meta-analysis by Jobard et al. (2003) associated activity in the left STG to the indirect route while the left MTG seems to be involved in both reading routes.

The part of the left STG that we observed to be directly affected by COMT genotype was specifically associated with the phonological analysis of words, a process that is based on sublexical mechanisms (Simos et al., 2000). Considering the very frequent occurrence in French of the words used during the task (*red, green, black* and *blue*), differences in regions associated with this indirect reading route were not expected. However, these differences represent changes in deactivation patterns driven mainly by the processing of neutral items. So, COMT-related changes in activity in that area do not seem to be specifically related to the Stroop effect and will not be discussed further. On the other hand, the left MTG appeared to be very close to the cerebral network associated with semantic access processes in the direct reading route (Fiebach et al., 2002; Jobard et al., 2003). Consequently, this region might be considered as part of the brain network that must be inhibited to perform the Stroop task efficiently.

How Can the Impact of COMT Genotype on Posterior Brain Areas and Their Functional Connectivity with the Right IFop in VV Participants Be Explained and Interpreted?

In a previous study, we showed that COMT genotypes had different effects on transient activity in anterior brain areas (VV > VM and MM in right IFop and SFG; VV and VM > MM in right IFop and cingulate areas) for interfering events in reactive control contexts (Jaspar et al., 2014). Here, we also show that posterior brain regions, especially temporal areas, are also affected by COMT Val^{158}Met polymorphism (VV > VM and MM in left MTG; VV and VM > MM in left STG). These different patterns of brain activation were obtained with analyses focusing on accurately processed stimuli. Thus, all group discrepancies observed and discussed at the brain activation level can be considered to be compensatory mechanisms set up by homozygous VV individuals to perform the task efficiently. In addition, we assume that these cerebral compensatory mechanisms can also be expressed by changes in brain functional connectivity (Cabeza & Dennis, 2012).

The observation of an influence of COMT polymorphism on temporal areas seems surprising at first glance. Indeed, the action of the COMT gene is mainly characterized by the degradation of dopamine in the frontal cortex (Karoum et al., 2004), but not really in posterior brain regions. On the basis of our psychophysiological analyses, we hypothesized that dopaminergic-mediated gating signals (influencing frontal activity and affected by COMT genotype) would impact the temporal areas associated with word processing via the right IFop. Indeed, we observed stronger positive functional connectivity between the right IFop and the left MTG in the homozygous Val carriers during the processing of interfering items. This pattern of results indicates that these participants recruit more of an area classically associated with interference resolution, the right IFop, than Met allele carriers (Garavan et al., 2002; Garavan et al., 1999; Konishi et al., 1999; Rubia et al., 2003), when an area associated with reading processes, the left MTG (Simos et al., 2000), is also highly activated. Interestingly, this observation is coupled with a stronger negative interaction between the right IFop and

the lingual gyrus for the same individuals; the latter region is involved in colour identification (Polk et al., 2008). Although these patterns of psychophysiological interactions cannot be directly interpreted in terms of causal effects by one area on another, we assumed that the lower DA level in the PFC for the homozygous VV group requires more involvement of PFC areas (right IFop and left PcG) to perform the task efficiently. As the right IFop is considered to have a braking function that can be turned on to pause an automatic response or to stop it outright (Aron et al., 2014), we propose that the stronger positive relationship observed between the right IFop and the left MTG reflects the right IFop's impact on temporal areas associated with reading; that influence may be direct or indirect. On the other hand, the negative relationship with the lingual gyrus cannot arise from a direct influence between these two areas if we consider the braking function attributed to the right IFop. Indeed, cognitive processes specific to the Stroop task and supported by the lingual gyrus (i.e., colour processing) are supposed to be enhanced, and not inhibited, during task performance. So we can suppose that the interaction between the right IFop and left lingual gyrus is mediated by a third (anterior or posterior) area that was not directly revealed by our PPI analysis.

As a whole, the results of this study indicate that the balance between the implementation of word reading and colour naming processes to perform the Stroop task correctly is specifically associated with activity in the right IFop in homozygous Val carriers. As activity in that area was previously associated with a less efficient physiological response in that population, this pattern of results can be interpreted as indicating less efficient regulation of processes that control colour naming and word reading. In agreement with this control hypothesis, activity in the right IFop is also positively associated with activity in the right superior frontal area. The right SFG is an area that has classically been linked to the Stroop effect (Laird et al., 2005) and is known to be a key area for rapid inhibitory control (Floden & Stuss, 2006). However, given our experimental design, the exact interrelationships between these anterior and posterior brain areas according to available DA level in frontal areas cannot be determined.

It would be particularly interesting to investigate this question using Dynamic Causal Modelling (DCM) analyses. Such analyses would allow a direct assessment of how the coupling parameters of the cerebral network observed here (right IFop, right STG, left MTG and right lingual gyrus) are modulated by COMT genotype (Kahan & Foltynie, 2013). In that context, the neural network model of dual control mechanisms developed by De Pisapia and Braver (2006) seems a particularly relevant starting-point to assess the (direct and indirect) excitatory and inhibitory influences of these four areas on each other, and how it depends of DA availability.

The main outcome of this study is the presence, during an inhibitory task, of an influence of COMT polymorphism on brain circuitry, as assessed by changes in anterior-posterior functional connectivity, and not just on prefrontal cortex. Similarly, two other studies showed decreased functional connectivity at rest between prefrontal regions and the posterior cingulate/retrosplenial cortices in homozygous Val individuals (Liu et al., 2010; Tian et al., 2013). Moreover, in the memory domain, Bertolino et al. (2006) showed that the number of Met alleles predicted the strength of relationship between the hippocampal formation and the ventrolateral prefrontal cortex during retrieval and (to a lesser extent) encoding of information. So, the influence of dopamine degradation in frontal areas on posterior brain networks could be a relatively general mechanism. Consequently, the exploration of the functional (and also structural) connectivity between anterior and posterior brain areas deserves a special attention in populations with dopamine depleted states, especially when a disconnection process was proposed as an explanation to cognitive deficits (i.e., in normal aging [Sullivan et al., 2001] or in schizophrenia [Friston, 1999].

Conclusion

In this study, we first demonstrated that variations in dopamine signalling mediated by COMT Val^{158}Met polymorphism influence anterior and posterior brain areas recruited to resolve interference. Indeed, homozygous VV individuals recruited more regions associated with executive functioning (right

IFop, left PcG) but also with non-executive functioning (left MTG and STG) than homozygous MM individuals when performing the Stroop task. In addition, PPI analyses demonstrated that COMT genotype also impacts functional connectivity between the right IFop (whose the function is braking automatic responses) and posterior brain areas associated with colour processing and reading. These genotype-related changes in cerebral activity and brain functional connectivity can be considered to be compensatory mechanisms developed by homozygous VV individuals so they can efficiently perform the task. Nevertheless, further studies are necessary to really understand the functional significance and generality of changes in brain connectivity evidenced here with an inhibitory task. The exploration of large samples of healthy participants using dynamic causal modelling analyses as well as functional and structural brain connectivity analyses in populations with dopamine depleted states appears particularly relevant to answer these questions.

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Table 1

General Interference Effect – Common Features between Comparisons by Genotype and Comparisons by Allele

Hemisphere	Anatomical Region	MNI Coordinates			Cluster Size	Z Score	P Value
		x	y	z			
Comparisons by genotype							
VV > MM							
L	Superior temporal gyrus	–62	–54	16	7	3.36	< .001
VM > MM							
L	Superior temporal gyrus	–60	–52	14	22	3.41	< .001
Comparisons by allele							
VV & VM > MM							
L	Superior temporal gyrus	–62	–54	16	70	3.85	< .0001
		–64	–44	16	70	3.48	< .001

Note. Local maxima of brain regions showing more transient brain activity for the interference effect (interfering vs. neutral items) 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 2

Interference Effect in Reactive Control Conditions – Common Features between Comparisons by Genotype and Comparisons by Allele

Hemisphere	Anatomical Region	MNI Coordinates			Cluster Size	Z Score	P Value
		x	y	z			
Comparisons by genotype							
VV > MM							
R	Inferior frontal operculum	60	–4	10	362	3.95	< .0001
L	Precentral gyrus	–62	0	14	10	3.38	< .001
L	Middle temporal gyrus	–54	–34	6	14	3.39	< .001
L	Superior temporal gyrus	–62	–46	18	68	3.66	< .001
VV > VM							
R	Inferior frontal operculum	54	16	–2	117	3.90	< .0001
L	Precentral gyrus	–62	4	16	11	3.46	< .001
L	Middle temporal gyrus	–54	–42	4	20	3.32	< .001
VM > MM							
L	Superior temporal gyrus	–58	–56	12	8	3.27	< .001
Comparisons by allele							
VV & VM > MM							
L	Superior temporal gyrus	–60	–56	12	264	3.64	< .0001
VV > VM & MM							
R	Inferior frontal operculum	56	10	–4	378	4.12	< .0001
L	Precentral gyrus	–62	2	16	95	3.58	< .001
L	Middle temporal gyrus	–54	–34	4	27	3.39	< .001

Note. Local maxima of brain regions showing more transient brain activity for the interference effect (interfering vs. neutral items) 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 3

PPI Analyses – Common Features between Comparisons by Genotype and Comparisons by Allele

Hemisphere	Anatomical Region	MNI Coordinates			Cluster Size	Z Score	P Value
		x	y	z			
Comparisons by genotype							
VV > MM							
R	Superior frontal gyrus	10	12	56	13	3.41	< .001
R	Cingulate gyrus	18	–6	40	23	3.73	< .001
L	Mid-cingulum	–8	–4	34	18	3.44	< .001
L	Middle temporal gyrus	–58	–40	8	236	3.61	< .001
R	Superior temporal gyrus	52	–24	2	86	3.36	< .001
L	Lingual gyrus	–18	–84	–10	124	3.89	< .0001
VV > VM							
R	Superior frontal gyrus	6	12	56	12	3.24	< .001
L	Mid-cingulum	–12	6	34	15	3.24	< .001
L	Middle temporal gyrus	–56	–42	6	196	3.96	< .0001
		–58	–32	2	196	3.31	< .001
L	Lingual gyrus	–32	–72	–4	100	3.52	< .001
VM > MM							
R	Cingulate gyrus	22	0	38	26	3.62	< .001
R	Superior temporal gyrus	52	–24	2	11	3.68	< .001
Comparisons by allele							
VV & VM > MM							
R	Cingulate gyrus	20	–2	38	21	3.47	< .0001
R	Superior temporal gyrus	52	–24	2	185	4.14	< .0001
VV > VM & MM							
R	Superior frontal gyrus	8	14	56	42	3.59	< .001
L	Mid-cingulum	–8	–4	34	27	3.51	< .001
L	Middle temporal gyrus	–58	–40	8	364	4.14	< .0001
		–52	–32	8	364	3.71	< .001
L	Lingual gyrus	–30	–70	–6	246	3.75	< .0001
		–22	–80	–10	82	3.56	< .001

Note. Local maxima of brain regions showing more transient brain activity for the interference effect (interfering vs. neutral items) 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); Sup. = Superior.

Figure Legends

Figure 1. Brain areas involved in interference resolution and differently affected by COMT genotype during the MC context. (a) Brain area showing a larger difference of activity between interfering (II) and neutral items (NI) for the Val allele carriers compared to homozygous Met carriers during the MC contexts; (b) Brain area showing a smaller difference of activity between interfering (II) and neutral items (NI) for the Met allele carriers compared to homozygous Val carriers during MC contexts. The regions are displayed on the T1 canonical image implemented in SPM8. See Table 2 for coordinates. (IFop = inferior frontal operculum; PcG = precentral gyrus; MTG = middle temporal gyrus; STG = superior temporal gyrus; MM = Met/Met participants; VM = Val/Met participants; VV = Val/Val participants).

Figure 2. Psychophysiological interactions between the interference effect (II–NI) and the right inferior frontal operculum. Brain areas showing a significantly greater psychophysiological interaction with the right IFop in the homozygous Val individuals. The regions are displayed on the T1 canonical image implemented in SPM8. See Table 3 for coordinates. (SFG = Superior frontal gyrus; Mid-cing. = Mid-cingulum; Cing. gy. = Cingulate gyrus; S/MTG = superior/middle temporal gyrus; Ling. gy. = Lingual gyrus; MM = Met/Met participants; VM = Val/Met participants; VV = Val/Val participants).

Figure 1

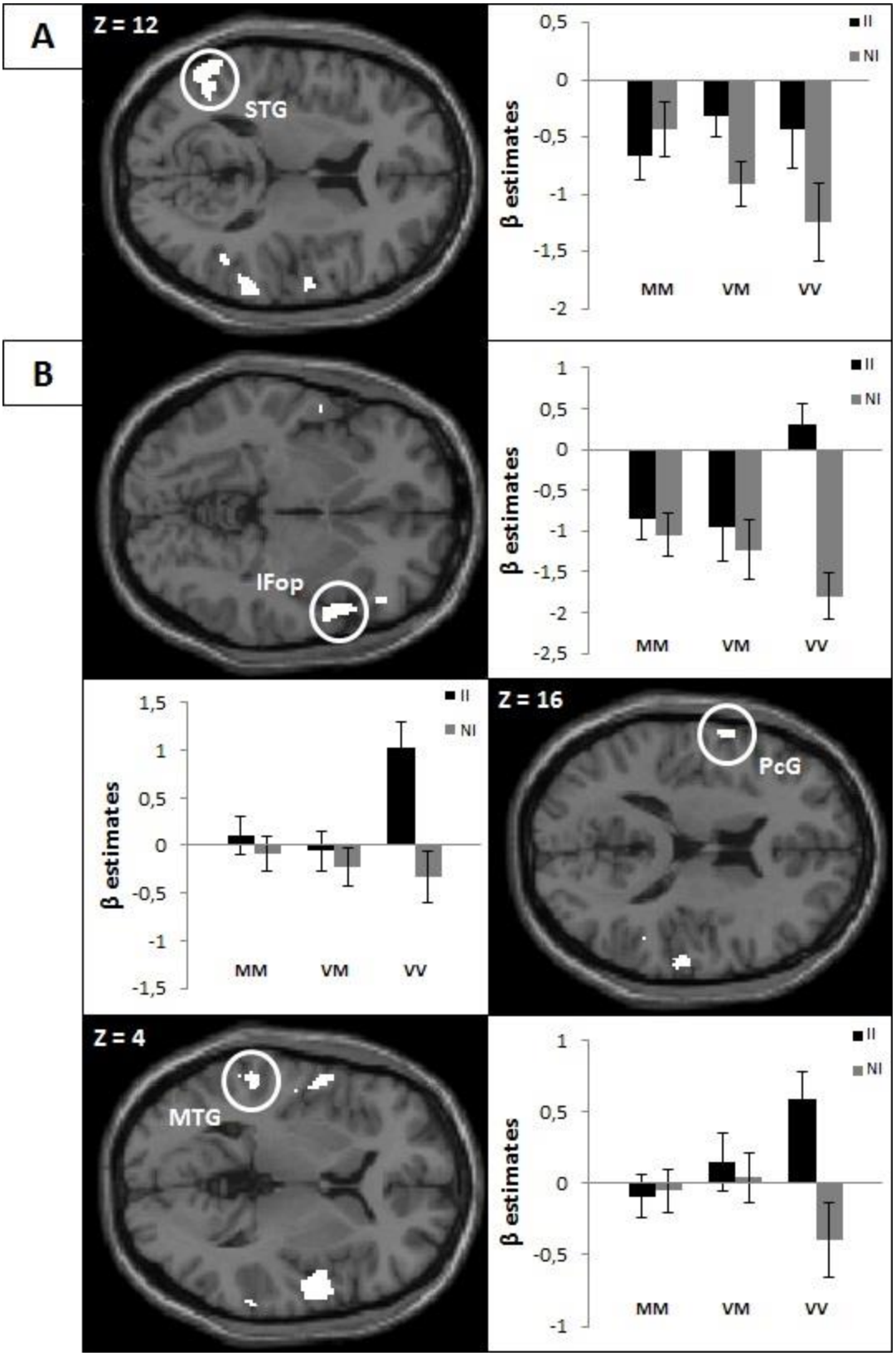
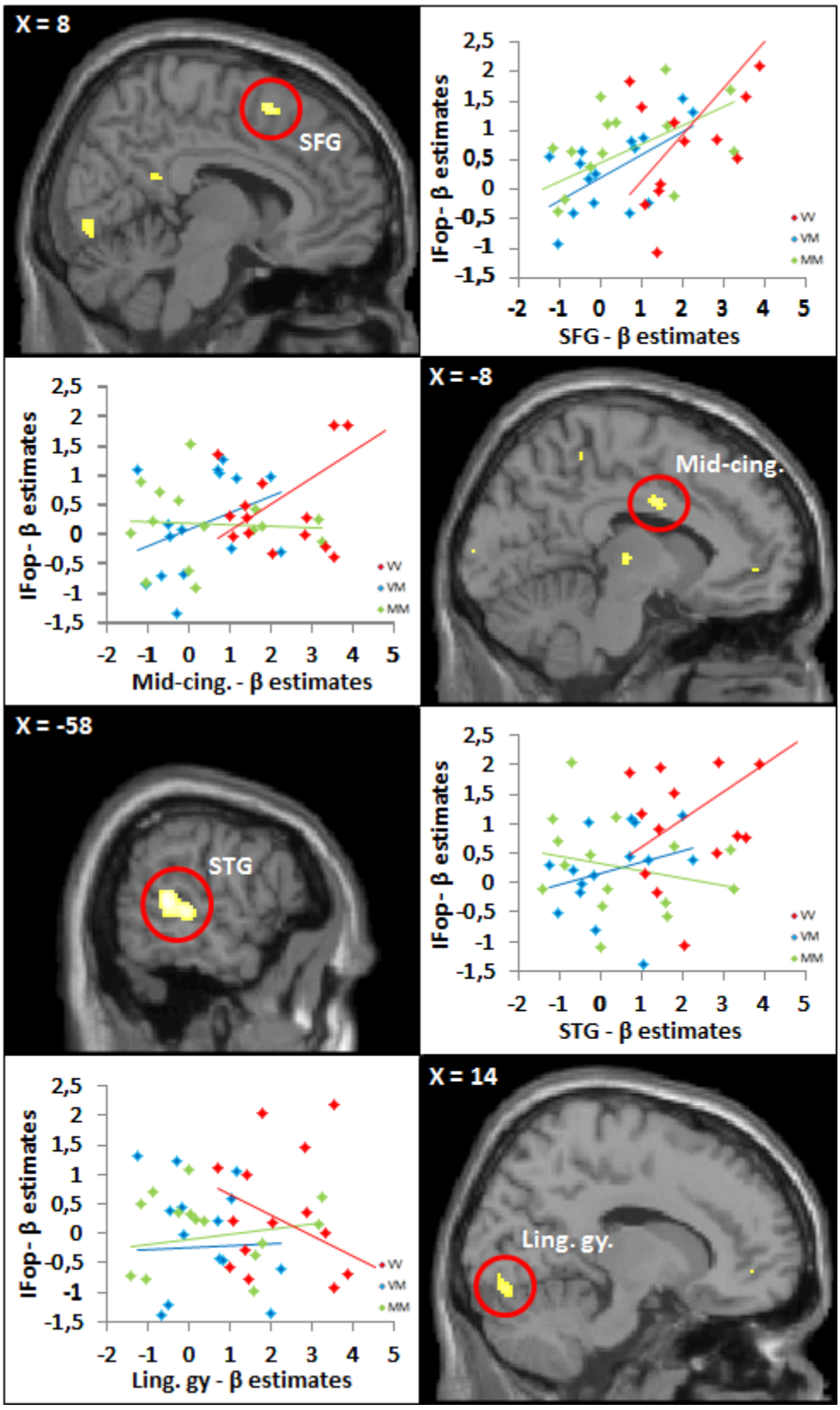


Figure 2.


X = 8
SFG
IFop- β estimates
SFG - β estimates
W
VM
MM
X = -8
Mid-cing.
Mid-cing. - β estimates
X = -58
STG
STG - β estimates
X = 14
Ling. gy.
Ling. gy - β estimates

SUPPLEMENTAL DATA

Methods

Participants

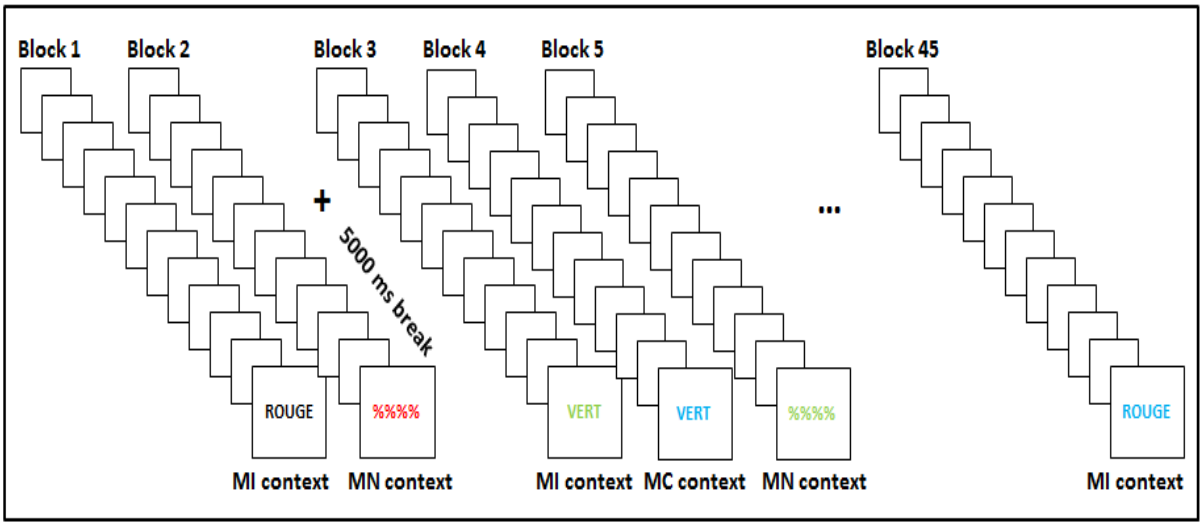
Table S1
Demographic Variables

	Val/Val (N=15)	Val/Met (N=15)	Met/Met (N=15)
Age	21.13 (2.33)	22.3 (2.94)	21.33 (2.38)
Raven matrices	54.33 (3.51)	55.20 (2.54)	53.13 (2.42)
Gender (M/F)	5/10	8/7	7/8

Note. Mean (standard deviation) for age and intelligence level (Raven's Advanced Progressive Matrices Test) and number of males and females in each group.

Materials and procedure

Figure S1
Schematic representation of the task design

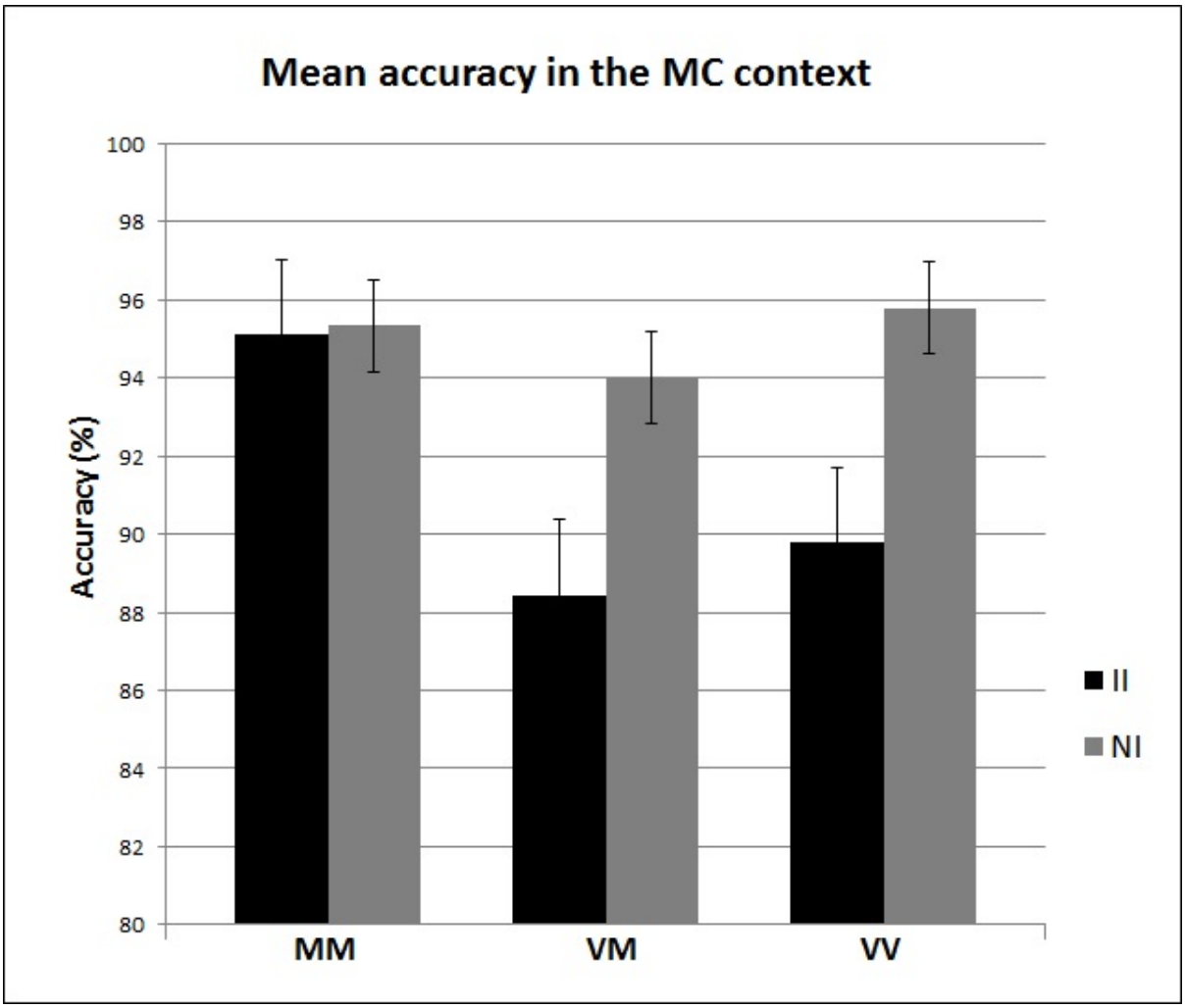


Note. The upper part of the figure shows the general procedure for context presentation (a fixation cross is presented after every two or three blocks of stimuli, with a total of 45 blocks) while the lower part covers the general procedure for item presentation (proportion of incongruent, congruent and neutral items as a function of block context). The letters B, N, V, R are the first letters, in French, of the four possible responses [B = *Bleu* ('Blue'); N = *Noir* ('Black'), V = *Vert* ('Green'), R = *Rouge* ('Red')].

Behavioural results

Figure S2

Mean accuracy in the MC context



Mean accuracy (%) in MM, VM and VV groups for incongruent (II) and neutral (NI) items in the mostly congruent context. Error bars represent standard deviations.

Fmri results

The neural substrates of the interference effect for the whole task

Table S2
General interference effect – Comparisons by Genotype.

Hemisphere	Anatomical region	MNI coordinates			Cluster size	Z score	P value
		x	y	z			
VV > MM							
L	Superior temporal gyrus	–62	–54	16	7	3.36	*< .001*
L		–38	–56	14	8	3 .32	< .001
VM > MM							
L	Superior temporal gyrus	–60	–52	14	22	3.41	< .001
VM > VV ; VV > VM ; MM > VM ; MM > VV Nothing							

Note. Local maxima of brain regions showing more activity in the incongruent than neutral items 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).

Table S3
General interference effect – Comparisons by Allele.

Hemisphere	Anatomical region	MNI coordinates			Cluster size	Z score	P value
		x	y	z			
VV & VM > MM							
L	Superior temporal gyrus	–62	–54	16	70	3.85	*< .0001*
L		–64	–44	16	70	3 .48	< .001
MM > VM & VV							
L	Middle occipital gyrus	–38	–72	0	9	3.29	< .001
MM & VM > VV							
L	Cerebellum	–16	–56	–34	15	3.39	< .001
VV > MM & VM Nothing							

Note. Local maxima of brain regions showing more activity in the incongruent than neutral items 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).

The neural substrates of the interference effect in the reactive control condition

Table S4

Interference effect in reactive control conditions – Comparisons by Genotype.

Hemisphere	Anatomical region	MNI coordinates			Cluster size	Z score	P value
		x	y	z			
VV > MM							
L	Mid. cingulum	–14	–28	46	11	3.35	< .001
R	Superior frontal gyrus	12	–20	70	9	3.40	< .001
R	Inferior frontal gyrus	48	36	0	7	3.23	< .001
R	Inferior frontal operculum	60	–4	10	362	3.95	< .0001
L	Precentral gyrus	–62	0	14	10	3.38	< .001
L	Inferior parietal lobule	–32	–40	46	42	3.48	< .001
L	Claustrum	–36	–20	2	18	3.33	< .001
R	Superior temporal gyrus	64	–36	10	234	4.38	< .0001
R		64	–20	12	234	3.71	< .001
R		50	–46	10	234	3.41	< .001
R		58	8	–4	362	3.99	< .0001
L		–62	–46	18	68	3.66	< .001
L	Middle temporal gyrus	–54	–34	6	14	3.39	< .001
L		–42	–60	12	75	3.61	< .001
VV > VM							
R	Inferior frontal operculum	54	16	–2	117	3.90	< .0001
L		–56	2	6	38	3.40	< .001
L	Precentral gyrus	–62	4	16	11	3.46	< .001
L	Middle temporal gyrus	–54	–42	4	20	3.32	< .001
L		–42	–76	6	16	3.41	< .001
L	Cuneus	–20	–86	28	15	3.15	< .001
R	Precuneus	14	–70	50	7	3.35	< .001
VM > MM							
R	Cingulate gyrus	12	6	40	8	3.24	< .001
L	Supramarginal gyrus	–60	–48	18	7	3.25	< .001
L	Superior temporal gyrus	–58	–56	12	8	3.27	< .001
MM > VM							
L	Middle occipital gyrus	–36	–88	–4	10	3.34	< .001
VM > VV ; MM > VV Nothing							

Note. Local maxima of brain regions showing more transient brain activity for the interference effect (interferent vs. neutral items) 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 conditions – Comparisons by Allele.

Hemisphere	Anatomical region	MNI coordinates			Cluster size	Z score	P value
		x	y	z			
VV & VM > MM							
R	Superior frontal gyrus	10	–20	70	7	3.37	< .001
R	Precentral gyrus	64	–4	8	37	3.45	< .001
R	Cingulate gyrus	12	6	40	21	3.43	< .001
L	Mid. cingulum	–14	–26	46	27	3.68	< .001
L	Insula	–36	–24	4	10	3.27	< .001
R	Inferior parietal lobule	60	–36	44	7	3.54	< .001
L	Parahippocampal gyrus	–42	–48	–8	6	3.27	< .001
L	Supramarginal gyrus	–62	–46	20	264	3.94	< .0001
R	Superior temporal gyrus	64	–36	14	94	3.76	< .001
R		48	–50	10	15	3.51	< .001
L		–60	–56	12	264	3.64	< .0001
L	Middle temporal gyrus	–52	–64	8	264	3.58	< .001
VV > VM & MM							
R	Inferior frontal operculum	56	10	–4	378	4.12	< .0001
R	Inferior frontal gyrus	50	34	–2	22	3.68	< .001
R	Precentral gyrus	58	–4	8	378	3.76	< .0001
R		50	2	4	378	3.40	< .001
L		–62	2	16	95	3.58	< .001
L		–56	0	6	95	3.39	< .001
R	Postcentral gyrus	64	–22	12	62	3.70	< .001
R	Superior temporal gyrus	64	–36	8	46	3.88	< .0001
R		50	–42	14	15	3.35	< .001
L		–58	–42	4	27	3.11	< .001
L		–60	–20	0	9	3.27	< .001
L	Middle temporal gyrus	–54	–34	4	27	3.39	< .001
L	Cuneus	–14	–80	32	10	3.27	< .001
MM > VV & VM ; MM & VM > VV							
Nothing							

Note. Local maxima of brain regions showing more transient brain activity for the interference effect (interferent vs. neutral items) 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).

Psycho-physiological interactions in the reactive control condition

Table S6
PPI analyses – Comparisons by Genotype.

Hemisphere	Anatomical region	MNI coordinates			Cluster size	Z score	P value
		x	y	z			
VV > MM							
R	Superior frontal gyrus	10	12	56	13	3.41	< .001
R	Middle frontal gyrus	26	–2	42	23	3.11	< .001
R	Precentral gyrus	32	–18	32	79	3.39	< .0001
L	Anterior cingulate	–10	42	18	24	3.34	< .001
R	Cingulate gyrus	18	–6	40	23	3.73	< .001
L	Mid-cingulum	–8	–4	34	18	3.44	< .001
R	Posterior cingulate	10	–46	22	13	3.48	< .001
L	Paracentral lobule	–8	–42	56	34	3.42	< .001
R	Superior temporal gyrus	44	–22	2	86	3.68	< .001
R		52	–24	2	86	3.36	< .001
R		42	–50	6	37	3.38	< .001
L		–58	–28	4	236	4.00	< .0001
L	Sup./middle temporal gyrus	–58	–40	8	236	3.61	< .001
L	Middle temporal gyrus	–36	–76	6	177	3.80	< .0001
L		–40	–72	16	177	3.35	< .001
R		34	–56	8	37	3.61	< .001
R		50	–68	12	12	3.35	< .001
L	Middle occipital gyrus	–24	–96	10	52	3.71	< .001
L		–14	–98	10	52	3.52	< .001
L	Lingual gyrus	–18	–84	–10	124	3.89	< .0001
R		14	–82	–8	86	3.57	< .001
R		6	–80	–8	86	3.27	< .001
VV > VM							
L	Superior frontal gyrus	–8	16	56	21	3.30	< .001
R		6	12	56	12	3.24	< .001
L	Mid-cingulum	–12	6	34	15	3.24	< .001
L	Cingulate gyrus	–24	–38	42	25	3.47	< .001
L	Sup./middle temporal gyrus	–56	–42	6	196	3.96	< .0001
L		–58	–32	2	196	3.31	< .001
L	Middle occipital gyrus	–36	–82	2	100	3.51	< .001
L	Lingual gyrus	–32	–72	–4	100	3.52	< .001
VM > MM							
R	Cingulate gyrus	22	0	38	26	3.62	< .001
R	Superior temporal gyrus	52	–24	2	11	3.68	< .001
R	Insula	36	–42	26	99	3.22	< .0001
VM > VV ; MM > VV ; MM > VM							
Nothing							

Note. Local maxima of brain regions showing stronger interactions with the right inferior frontal gyrus when II and NI are contrasted in the MC context (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

PPI analyses – Comparisons by Allele.

Hemisphere	Anatomical region	MNI coordinates			Cluster size	Z score	P value
		x	y	z			
VV & VM > MM							
R	Cingulate gyrus	20	–2	38	21	3.47	< .0001
L	Posterior cingulate	–30	–72	8	84	3.25	< .001
R	Precentral gyrus	32	–20	38	107	4.22	< .001
R	Superior temporal gyrus	52	–24	2	185	4.14	< .0001
R		44	–22	2	3.87	185	< .0001
R		42	–48	6	76	3.51	< .001
R		40	–52	22	117	3.40	< .001
L		–58	–28	4	14	3.28	< .001
R	Middle temporal gyrus	34	–56	8	76	3.69	< .001
L		–36	–72	14	84	3.70	< .001
R	Parahippocampal gyrus	24	–52	6	76	3.25	< .001
R	Insula	36	–44	26	117	3.83	< .0001
L	Middle occipital gyrus	–38	–74	6	84	3.49	< .001
R	Thalamus	20	-8	–4	13	3.38	< .001
R	Culmen	14	–52	–24	30	3.58	< .001
VV > VM & MM							
R	Superior frontal gyrus	8	14	56	42	3.59	< .001
L	Anterior cingulate	–6	52	–2	14	3.21	< .001
R	Mid-cingulum	–8	–4	34	27	3.51	< .001
R	Cingulate gyrus	–16	–34	38	25	3.20	< .001
L		–22	–38	42	25	3.49	< .001
R	Posterior cingulate	10	–44	20	15	3.42	< .001
L	Superior temporal gyrus	–58	–30	2	364	3.91	< .0001
L	Sup./middle temporal gyrus	–58	–40	8	364	4.14	< .0001
L		–52	–32	8	364	3.71	< .001
R	Middle temporal	50	–70	14	14	3.43	< .001
L		–50	–66	16	56	3.40	< .001
L	Middle occipital	–38	–80	6	246	3.72	< .0001
L		–24	–96	10	246	3.80	< .0001
L		–10	–98	10	11	3.67	< .001
R	Lingual gyrus	14	–82	–12	94	3.44	< .001
L		–30	–70	–6	246	3.75	< .0001
L		–22	–80	–10	82	3.56	< .001
L	Insula	–38	–34	18	79	3.42	< .001
L	Thalamus	–10	–20	4	27	3.71	< .001
MM > VV & VM ; MM & VM>VV Nothing							

Note. Local maxima of brain regions showing stronger interactions with the right inferior frontal gyrus when II and NI are contrasted in the MC context (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).

Psycho-physiological interactions in the reactive control condition with gender used as covariate

Table S8

PPI Analyses – Common Features between Comparisons by Genotype and Comparisons by Allele using gender as covariate.

Hemisphere	Anatomical Region	MNI Coordinates			Cluster Size	Z Score	P Value
		x	y	z			
Comparisons by genotype							
VV > MM							
R	Superior frontal gyrus	10	12	56	9	3.33	< .001
R	Cingulate gyrus	18	–6	40	15	3.64	< .001
L	Mid-cingulum	–8	–4	34	13	3.35	< .001
L	Middle temporal gyrus	–58	–40	8	208	3.49	< .001
R	Superior temporal gyrus	44	–22	2	75	3.66	< .001
L	Lingual gyrus	–18	–84	–10	97	3.75	< .0001
VV > VM							
R	Superior frontal gyrus	6	12	56	2	3.23	< .001
L	Mid-cingulum	–10	6	34	2	3.12	< .001
L	Middle temporal gyrus	–56	–42	6	146	4.14	< .0001
		–58	–30	0	146	3.27	< .001
L	Lingual gyrus	–30	–72	–4	12	3.56	< .001
VM > MM							
R	Cingulate gyrus	22	0	38	13	3.66	< .001
R	Superior temporal gyrus	52	–24	2	26	3.66	< .001
Comparisons by allele							
VV & VM > MM							
R	Cingulate gyrus	20	–2	38	22	3.44	< .001
R	Superior temporal gyrus	52	–24	2	174	4.08	< .0001
VV > VM & MM							
R	Superior frontal gyrus	8	14	56	32	3.55	< .001
L	Mid-cingulum	–8	–4	34	18	3.41	< .001
L	Middle temporal gyrus	–58	–40	8	321	4.00	< .0001
		–52	–32	8	321	3.60	< .001
L	Lingual gyrus	–30	–70	–6	176	3.59	< .001
		–22	–80	–10	42	3.40	< .001

Note. Local maxima of brain regions showing more transient brain activity for the interference effect (interfering vs. neutral items) during MC blocks at a voxel *p* value < .001 uncorrected when gender is used as covariate.

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