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Modulating effect of COMT genotype on the brain regions underlying proactive control process during inhibition

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Abbreviated title: COMT and neural bases of cognitive control

Abstract

Introduction. Genetic variability related to the catechol-O-methyltransferase (COMT) gene (Val158Met polymorphism) has received increasing attention as a possible modulator of cognitive control functions.

Methods. In an event-related fMRI study, a modified version of the Stroop task was administered to three groups of 15 young adults according to their COMT Val158Met genotype [Val/Val (VV), Val/Met (VM) and Met/Met (MM)]. Based on the theory of dual mechanisms of control (Braver, et al., 2007), the Stroop task has been built to induce proactive or reactive control processes according to the task context.

Results. Behavioral results did not show any significant group differences for reaction times but Val allele carriers individuals are less accurate in the processing of incongruent items. fMRI results revealed that proactive control is specifically associated with increased activity in the anterior cingulate cortex (ACC) in carriers of the Met allele, while increased activity is observed in the middle frontal gyrus (MFG) in carriers of the Val allele.

Conclusion. These observations, in keeping with a higher cortical dopamine level in MM individuals, support the hypothesis of a COMT Val158Met genotype modulation of the brain regions underlying proactive control, especially in frontal areas as suggested by Braver et al.

Keywords: inhibition – cognitive control – fMRI – COMT gene – Stroop Task

1. Introduction

Several lines of evidence suggest that the neurotransmitter dopamine (DA) plays an important role in human cognition. Indeed, a dysfunction in dopamine systems is observed in pathological conditions associated with cognitive deficits such as Parkinson's disease or schizophrenia (Heinrichs and Zakzanis, 1998; Moustafa and Gluck, 2011; Tunbridge, et al., 2006). Moreover, psychopharmacological studies showed that administration of dopaminergic drugs could result in opposite effects on cognitive performance (Cools and D'Esposito, 2011), notably during working memory or set-shifting tasks (Kimberg, et al., 1997; Mattay, et al., 2003; Mehta, et al., 2000). Indeed, administration of dopamine drugs is associated with a positive or negative effect on cognition, depending on whether baseline cognitive efficiency level is low or high, respectively. These findings lead Cools and Robbins [(Cools and Robbins, 2004); see also (Cools and D'Esposito, 2011)] to propose a model in which the relationship between cognitive performance and DA level follows an *'inverted-U-shaped'* function, defining an optimal DA level for any given cognitive task.

The major mechanism by which the synaptic activity of dopamine is terminated is reuptake, followed by metabolic degradation. Catechol O-methyltransferase (COMT) is the major enzyme involved in the metabolic degradation of released dopamine and accounts for more than 60% of the metabolic degradation of dopamine in the frontal cortex (Karoum, et al., 1994). The human COMT gene is located on the long arm of chromosome 22q11 (Männistö and Kaakkola, 1999) and contains a functional polymorphism in codon 158 (Val^{158}met) affecting the activity of the enzyme (Chen, et al., 2004; Lachman, et al., 1996). A transition of guanine to adenine results in a valine to methionine substitution which leads to different COMT genotypes. Each genotype is associated with different COMT enzymatic activity such that the enzyme containing Met^{158} is significantly less active than the Val^{158} enzyme, potentially resulting in a greater synaptic dopamine level (Chen, et al., 2004; Lotta, et al., 1995). Consequently, individuals homozygous for Met allele (MM) are those with the highest

level of cerebral synaptic dopamine whereas homozygous for Val allele (VV) have the lowest level. Heterozygote (VM) carriers exhibit an intermediate level of COMT activity (Weinshilboum, et al., 1999).

The role of catechol-*o*-methyltransferase (COMT) in modulating high-level cognitive processes (such as executive functions) and their neural substrates was reported in several studies. The impact of COMT genotype was frequently reported on behavioral performance when multi-compound executive tasks were administered, such as the Wisconsin Card Sorting Test or planning and decision making tasks. Most of these studies reported a better performance in the Met allele carriers population (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; Roussos, et al., 2007). However, when tasks assessing more specific executive processes were used, the advantage related to the Met polymorphism was not so obvious. For instance, no effect of the polymorphism was observed on the Trail-Making test, verbal fluency, digit span backward go/no-go and n-back tasks (Barnett, et al., 2008; Bertolino, et al., 2006; Ho, et al., 2005; Stokes, et al., 2011).

Nevertheless, neuroimaging studies clearly showed a modulating effect of the COMT polymorphism on brain responses involved in executive performance. Bertolino et al. (2006), using a 2-back working memory task, showed that MM individuals had a more focused response (lesser activation for similar performance) in a network of brain areas (left precentral gyrus, middle frontal gyrus [MFG] bilaterally and anterior cingulated cortex [ACC]) previously associated with working memory [for globally similar results see Egan et al. (2001)]. With regard to interference control, Blasi and collaborators (2005) used a perceptual conflict task to assess attentional control. They observed a larger activity in the cingulate cortex, related to decreased accuracy performance, in homozygous VV individuals by comparison to VM heterozygous who in turn showed greater activity and poorer performance than MM individuals. Moreover, these effects are the most evident in the highest attentional demand condition. Using a Stop-signal task, Congdon et al. (2009) observed larger

activity in Met allele carriers in a frontostriatal network associated with response inhibition (Aron, et al., 2004). As the three groups obtained a similar behavioral performance and several fMRI studies of the Stop-signal task have demonstrated that greater activation represents better inhibitory control in that task (Aron and Poldrack, 2006; Li, et al., 2006), the authors concluded that neural response might be impaired in homozygous Val participants by comparison to VM and MM individuals. The apparent discrepancy between the absence of effect on specific behavioral measures and the modulating effect of COMT genotype on brain areas associated with executive processes can be explained by a better sensitivity of neuroimaging techniques. Indeed, these techniques characterize genetic effects at the level of neural circuitry and are thus less influenced by environmental variables such as alternative strategies, level of cooperation, etc. (Mattay, et al., 2008).

Collectively, these imaging and behavioral data suggest a less-efficient physiological response in prefrontal cortex during information processing in individuals homozygous or heterozygous for the Val allele. In other words, brain imaging studies showed that Val allele carriers need greater prefrontal activity for comparable levels of performance, indicating less efficient cognitive functioning in these individuals.

In the present study, we were interested in exploring the modulating effect of COMT genotype on brain regions underlying cognitive control, a high-level cognitive process related to executive functioning. Cognitive control refers to our ability to flexibly adjust our behavior depending on situational demands and changes in the environment, especially in situations where distracting information or a predominant response tendency must be ignored in order to successfully act in a goal-oriented manner. Braver, Gray and Burgess (2007) developed a general theory of cognitive control, the Dual Mechanism of Control (DMC) account, which states that flexibility in cognitive control strategies, depending on situational demands or individual differences, may be achieved through reactive or proactive control. Proactive control is postulated to be a sustained form of control that can be engaged in situations in which the upcoming stimulus can be anticipated,

allowing rapid and efficient responses. More specifically, proactive control involves active maintenance of all task-relevant information (i.e., task instructions, identity of previous stimuli, cues for later behavior, etc.) that could be useful to produce an appropriate response to cognitively demanding events. Reactive control, on the other hand, is thought to be engaged in situations in which anticipating the characteristics of the upcoming stimuli is not the most efficient way of performing the task. In that case, the occurrence of a critical event triggers the reactivation of required information in a transient manner, specifically to that critical stimulus. In sum, the DMC model suggests that proactive control mechanisms are specialized in the interference prevention and anticipation, whereas reactive control is dedicated to detect and resolve interference at the moment of his occurrence. An important factor which can modulate the extent to which proactive or reactive strategies contribute to task performance is the overall task context (i.e., task demands and characteristics). Indeed, whereas both strategies are equally likely to lead to correct performance on a specific trial, there are some situations in which one or the other kind of control would be most appropriate, with task context encouraging the adoption of one form of control over the other. Among the situational factors prone to favor specific control strategy, conditions involving high interference level and allowing the anticipation of interference effects should encourage the use of proactive control (Braver, et al., 2007). Therefore, under situations in which interference is infrequent and unexpected, reactive control mechanisms are predicted to dominate. In contrast, when interference is relatively frequent and can be reasonably anticipated, there may be a greater tendency for proactive control to emerge.

Importantly, both mechanisms of control are supposed to be clearly dissociable according to the underlying brain regions and the temporal pattern of this neural activity (Braver, 2012; Braver, et al., 2007; De Pisapia and Braver, 2006). Proactive control is supposed to be associated with sustained activation of lateral prefrontal cortex, which would reflect the active maintenance of tasks' goals and instructions. For reactive control, lateral prefrontal cortex should be engaged in a transient manner when interference is detected and would reflect reactivation of task goals. Importantly, a wider

network of additional brain regions typically associated with conflict detection and monitoring, especially the ACC, is also expected to play a crucial role for reactive control. Braver et al. (Braver, et al., 2007) also proposed that the two control mechanisms should differ in terms of involvement of the dopaminergic system (DA system). The ability to actively sustain inputs in lateral prefrontal cortex requires a phasic dopaminergic-mediated gating signal occurring at the time when contextual cues are presented. Without such gating signal, the prefrontal cortex can only be transiently activated, which leads to a reactive form of cognitive control. Consequently, COMT genotype could be an individual variable influencing the effective implementation of proactive and reactive control processes. If only the implementation of proactive control is related to the availability of dopamine in prefrontal areas, individuals carrying at least one Met allele should be advantaged when the task context requires proactive control.

At this time, two studies focused on the neural substrates of proactive and reactive cognitive control processes. Using the recent probe task assessing sensitivity to interference in working memory, Burgess and Braver (2010) compared brain areas related to interference in low (few interfering items) and high (many interfering items) expectancy conditions. As expected, different pattern of brain activity were associated with proactive and reactive control mechanisms according to interference expectancy. More precisely, in the low expectancy condition, the inferior prefrontal cortex bilaterally [as well as the left dorsolateral prefrontal cortex (DLPFC), the right pre-supplementary motor area (pre-SMA) and the left lateral parietal lobule] exhibited a probe-triggered increase in activity, specifically on interfering items, consistent with recruitment of reactive control. By contrast, in the high expectancy condition, activity in the left MFG increased during the delay period, prior to probe onset, with this effect occurring both on interfering and non-interfering trials, which is consistent with a proactive control strategy. In a second study, the neural substrates of proactive and reactive cognitive control processes were investigated using the Stroop task (Grandjean, et al., 2012). Manipulating the proportion of interfering and facilitator items, two experimental conditions were created: the mostly incongruent (MI) and mostly congruent (MC)

contexts, respectively. A reactive control strategy, which corresponds to transient interference resolution processes after conflict detection, was expected for rare conflicting stimuli in the MC context, and a proactive strategy, characterized by a sustained task relevant focus prior to the occurrence of conflict, was expected in MI context. Reactive control for incongruent trials in MC context engaged a fronto-parietal network including DLPFC and ACC. However, proactive control during MI context was not associated with any sustained lateral PFC activations. Surprisingly, incongruent trials of MI context elicited transient activation in common with incongruent trials of MC context, especially in DLPFC, superior parietal lobe, and insula.

Aim of the study and prior hypotheses

The aim of this study was to determine the modulating effect of COMT genotype on the brain regions underlying proactive and reactive cognitive control processes during a Stroop inhibition task. According to the DMC model (Braver, 2012; Braver, et al., 2007), proactive control would be associated with sustained activation of the lateral PFC, reflecting the active maintenance of task goals and instructions. Moreover, active maintenance of task relevant contextual information within lateral PFC would be regulated by the DA system. Consequently, we predicted that carriers of the Val allele of COMT (with the higher enzymatic activity and thus less DA available) will be less efficient in the use of proactive control. Therefore, a more extensive recruitment of the lateral PFC will be necessary in the Val allele carriers to reach the same performance as the carriers of the Met allele in this specific context. Moreover, from a behavioral point of view, more accurate and faster performance can be expected in the Met allele carriers'. Finally, we expected no effect of COMT related dopamine level on reactive control processes.

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

One hundred and six Caucasians 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 color vision. Each participant was also screened for any physical or medical condition that could prevent an MRI session. Through a DNA screening, our sample has been 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). 15 subjects were selected in each group in order to match them for gender [$F(2) = .60$; $p = .55$], age [$F(2) = .94$; $p = .40$] and fluid intelligence level [$F(2) = 1.96$; $p = .15$] (see Table 1). Fluid intelligence level was estimated using Raven's advanced progressive matrices test (Raven, et al., 1983).

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

2.4. Materials & procedure

A modified form of the Stroop task (Grandjean, et al., 2012) with four words presented on a white background (Red, Blue, Black, and Green) was used for this experiment. Proportion congruency was manipulated using three different contexts of 12 items each (see Figure 1): the *mostly congruent context* (MC), the *mostly incongruent context* (MI), and the *mostly neutral context* (MN). Each MI block was composed of 8 incongruent items (or interfering items, e.g. the word "red" written in blue), 2 congruent items (or facilitators items, e.g. the word "blue" in blue), and 2 neutral items, which were non-verbal stimuli (i.e., strings of five percent signs %%%%%) presented in one of the four color 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 in the beginning of each MI context) and served 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.

[INSERT FIGURE 1]

The participants were instructed to indicate the color 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. Color words were presented on a screen that the participants, lying into the fMRI scanner, viewed through a mirror located on the scanner's head coil. Each trial consisted of the presentation of a word at the center of the screen, with four response possibilities at the bottom of the screen (corresponding to the four color possibilities, always in the same order). Each item was presented until the participant responded (with a maximum presentation time of 2000 msec). 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 msec. The inter-stimulus interval set to 500 msec. A fixation cross was presented at the center of the screen for 5000 msec after every two or three contexts to provide breaks during the experiment (see Figure 1).

Prior to the MRI session, participants performed a practice session outside the scanner in which 40 items were presented to ensure 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.

2.5. Behavioral data analysis

All behavioral data analyses were conducted with a statistical level set at $p<.05$. Repeated measures ANOVAs were run on the median RTs and accuracy data (errors and no responses), with task context (MC, MI, and MN contexts) and item type (incongruent, congruent, and neutral items) as repeated measures factors. We also reported partial eta squared (η_p^2) as a measure of effect size. Finally, planned comparisons were performed, also with a $p<.05$, using univariate tests of significance.

2.6. *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 = 220x220 mm^2, voxel size 3.4x3.4x3 mm^3, 30% interslice gap, matrix size 64x64x32, 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.

Data were preprocessed and analyzed 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 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 10-mm full-width at half-maximum (FWHM) Gaussian kernel.

For each participant, BOLD responses were modeled at each voxel, using a general linear model with events convolved with the canonical hemodynamic response function as regressors. Events were divided according to the three contexts (MI, MC, or MN context) and the type of item (incongruent, congruent, or neutral). These 9 regressors were modeled as event-related responses. Event durations corresponded to the presentation of the item until the participant's response, with a maximum duration of 2 sec. Incorrect trials and no responses were also modeled 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 modeled 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 sec 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. All analyses were conducted using a correction for

multiple comparisons at the voxel level with a conservative family-wise error (FWE) threshold $p < 0.05$.

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 (i.e., general interference effect in the three contexts, interference effects in the mostly congruent and mostly incongruent contexts separately, comparison of brain activity across the MI vs. the MC context). First, these individual contrasts images were used to analyze neural activity common to the three genotype groups. Second, we focused on genotype-related differences on the neural correlates of proactive and reactive control processes. T-tests comparisons between VV, VM and MM groups were performed. Only the analyses assessing between-group comparisons of the neural substrates of proactive and reactive cognitive control processes are detailed in the main text. These analyses consisted in the exploration of brain areas showing (1) sustained activity in the mostly incongruent by comparison to the mostly congruent condition and (2) transient activity for interferent items in the mostly incongruent and mostly congruent conditions respectively. 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. We will consider as relevant for the discussion only brain areas that are consistently found significant across these two analyses. Results of the following analyses are reported in supplemental data for sake of completeness: 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 MI (transient and sustained activity) and MC (transient activity) contexts.

Given the a priori hypothesis regarding specific anatomical loci of interest, we adopted a region-of-interest (ROI) approach to limit the scope of our analyses. These loci were the lateral prefrontal cortex (PFC) for the sustained response related to proactive control and the lateral prefontal and anterior cingulate cortex (ACC) for the transient responses associated with reactive control (Braver,

2012). Regions-of-interest (ROIs) covering lateral PFC and ACC were anatomically defined and created on the basis of the WFU PickAtlas software (Maldjian, et al., 2003). The ROIs encompassed both lateral (superior, inferior and middle frontal gyrus) and medial (including anterior and mid cingulate cortex) portions of the frontal lobes. These subregions were combined to create one PFC ROI, with a size of 370mm^3. For each between-group contrast, the ROI was used as a mask for interrogation of differentially activated voxels within SPMs thresholded at $p < .001$, uncorrected. The extent threshold was set to 10 contiguous voxels.

3. **Results**

3.1. Behavioral results

We conducted a repeated 3 (context) x 3 (item) analysis of variance (ANOVA) on median reaction times (RTs) for correct responses with the group as an independent variable. We observed a significant main effect of item [$F(2,84) = 207.3$; $p < .0001$; $\eta_p^2 = .83$] and a significant main effect of context [$F(2,84) = 20.99$; $p < .0001$; $\eta_p^2 = .33$], but no significant main effect of group [$F(2,42) = .65$; $p = .53$; $\eta_p^2 = .03$] (see Figure 2a). Planned comparisons showed that the item effect was characterized by slower RTs for incongruent than for congruent [$F(1,42) = 310.06$; $p < .0001$] or neutral [$F(1,42) = 200.70$; $p < .0001$] items. The context effect was characterized by faster RTs in MI than in MC [$F(1,42) = 8.20$; $p < .01$] and MN [$F(1,42) = 36.81$; $p < .0001$] contexts, but also by better reaction time in MC than MN context [$F(1,42) = 14.55$; $p < .0005$]. An interaction effect between context and item was also observed [$F(4,168) = 7.32$; $p < .001$; $\eta_p^2 = .15$] (See Supplemental Data for details). These behavioral effects are similar to those reported by Grandjean et al. (2012).

[INSERT FIGURE 2]

As for reaction time, a 3 (context) x 3 (item) analysis of variance (ANOVA) on item accuracy with the group as an independent variable was performed. The pattern of results in term of item and context

effects is the same than for RTs (See Supplemental Data for detailed results). With regard to the genotype, no significant group effect was found for item accuracy [F(1,42) = 1.51 ; p = .23 ; η_p^2 = 0.07]. Nevertheless, a significant item x group interaction [F(4,84) = 2.77 ; p < .05 ; η_p^2 = .12] was observed. Planned comparison showed a smaller decrease in performance from the neutral to the incongruent items in the MM group by comparison to VM [F(1,42) = 4.85 ; p = .03] and VV [F(1,42) = 6.37 ; p = .02] groups (see Figure 2b).

3.2. fMRI results

3.2.1. General interference effect

First of all, the general interference effect (i.e., incongruent vs. neutral items) across the three contexts revealed a large map of activation corresponding to the extensive fronto-parietal network typically associated with interference resolution in the Stroop task (see Table S1). More specifically, we found more brain activity in ACC, DLPFC, inferior parietal regions, but also in the insula and cerebellum when incongruent items were presented. This network of areas has already been evidenced in a previous study using the same task procedure (Grandjean, et al., 2012).

3.2.2. Cognitive control and interference effect

With regard to transient activity related to incongruent items in proactive control condition, increased brain activity was observed in the right cerebellum only. Conversely, incongruent items in the reactive control condition were associated with activity in a network of fronto-parietal areas and also in the insula and cerebellum. Finally, the comparison of sustained brain activity in the MI versus the MC context, also reflecting proactive control processes, did not shown significant difference between conditions. Again, the results obtained here are similar to those reported by Grandjean et al. (2012) and are detailed in Table S2.

3.2.3. Influence of genotype on the brain regions associated with proactive control processes

Sustained brain activity during the MI condition (by comparison to the MC condition) was compared between the VV, VM and MM groups of participants (see Table 2). The MM genotype showed, by comparison to the VV genotype, increased brain activity in the right anterior cingulate and mid-cingulate gyrus. The reverse comparison (VV>MM) showed increased brain activity in the left middle frontal gyrus. With regard to the VM group, more activity was observed by comparison to the MM group in the left inferior frontal triangularis gyrus and left middle frontal gyrus; and, by comparison to the VV group, in the right anterior and left mid cingulate gyrus, in the medial superior frontal gyrus bilaterally, in the right middle frontal gyrus and in the left inferior/orbital frontal gyrus. The comparisons of the VV to VM groups and the MM to VM groups did not show any significant results.

[INSERT TABLE 2]

In order to better specify the influence of carrying a Val or Met allele respectively, we compared (1) brain activity in MM and VM groups to the activity in the VV group, and (2) the activity of the VV and VM groups to that in the MM group (see Table 3 and Figure 3). Brain areas more activated in the carriers of at least one Met allele by comparison to homozygous carriers of the Val Allele (MM and VM > VV) are the right anterior and mid cingulate gyrus, the left medial superior frontal gyrus, the right middle frontal gyrus and the left inferior/orbital frontal gyrus. The carriers of at least one Val allele showed more activity, by comparison to homozygous carriers of the Met allele (VV and VM > MM), in the left middle frontal gyrus. No significant results were obtained for the reverse comparisons (neither for MM and VM < VV nor for VV and VM < MM).

[INSERT TABLE 3 AND FIGURE 3]

Transient brain activity specific to incongruent items (by comparison to neutral ones) in the MI condition was compared between the VV, VM and MM groups of participants. The comparison of the three groups (VV vs. MM, VM vs. VV and VM vs. MM) as well as the comparison of the groups carrying at least one Val or Met allele (MM vs. VV and VM; VV vs. VM and MM) did not show significant difference in brain activity.

Results of these analyses can be summarized in the following way. With regard to sustained activity, carrying a Met allele was consistently associated with larger brain activity in the right anterior and mid-cingulate gyrus. On the contrary, more brain activity was consistently observed in the left middle frontal gyrus when participants were carrying at least one Val allele. Finally, no significant group difference was found for transient brain activity related to incongruent items in a context inducing proactive control.

3.2.4. Influence of genotype on the brain regions associated with reactive control processes

Here, we compared, between the VV, VM and MM groups of participants, the transient pattern of cerebral activity for incongruent items (by comparison to neutral ones) in the MC context (see Table 4). The VV genotype showed increased brain activity in the right inferior frontal operculum by comparison to the MM genotype and also bilateral increased activity in that area by comparison to the VM group. The reverse contrasts (MM>VV and VM>VV) showed no significant brain activity and such an absence of significant results was also observed for the comparisons VM>MM and MM>VM.

[INSERT TABLE 4]

Again, in order to better specify the influence of carrying a Val or Met allele respectively, we compared (1) brain activity in MM and VM groups to the activity in the VV group, and (2) the activity of the VV and VM groups to that in the MM group (see Table 5 and Figure 4). Brain areas more activated in the group of carriers of at least one Val allele (by comparison to the homozygous Met allele group) were the right anterior cingulate, the left mid-cingulum and the right frontal operculum. Homozygous carriers of the Val allele showed (by comparison to carriers of at least one Met allele) increased brain activity in the inferior frontal operculum bilaterally, the right inferior frontal triangularis and left superior frontal gyrus. No significant results were obtained for the comparisons MM and VM > VV, and VV and VM < MM.

To summarize, the main results of analyses on transient activity related to reactive control processes evidenced that the number of Val alleles was positively associated with brain activity in the inferior frontal operculum (with the VV participants having the highest activity). We can also, more tentatively, report that carrying at least one Met allele was also associated, but less consistently, to decreased activity in the right inferior triangularis and left superior frontal gyrus.

[INSERT TABLE 5 AND FIGURE 4]

4. Discussion

The objective of this study was to determine if the COMT genotype is associated with differential patterns of brain responses when the task requires proactive and reactive cognitive control processes. First, at a behavioral level, we observed a globally similar pattern of performance in the three genotypes regarding RTs. However, Val allele carriers provided more erroneous responses for incongruent trials than Met homozygous participants, suggesting larger sensitivity to interference whatever the task context. It is noteworthy that the decreased accuracy for incongruent events in the Val allele carriers group was obtained although the groups of participants were matched on age, IQ and other demographic factors. Interestingly, the absence of significant interaction effect between genotype and task condition (proactive vs. reactive control) allowed us to discuss brain imaging data by excluding the influence of different level of task difficulty across groups. With regard to the neuroimaging data, when the task context requires the implementation of proactive control (in the MI context), carrying a Met allele was consistently related to larger sustained brain activity in the right anterior and mid-cingulate gyrus (comparisons MM>VV, VM>VV, MM and VM>VV). On the contrary, in participants carrying at least one Val allele, a larger brain activity in the left middle frontal gyrus was consistently observed (VV>MM, VM>MM, VV and VM>MM). When transient activity associated with interfering items in the MI context was compared between the three groups, no significant group difference was observed. As for reactive control, the presence of Val allele(s) was mainly related to higher brain activity in the inferior frontal operculum.

4.1.The role of dopamine in the implementation of proactive cognitive control processes

According to the DMC model (Braver, 2012; Braver, et al., 2007), proactive control would be associated with sustained brain activity in the lateral PFC (reflecting the active maintenance of task relevant contextual information) that requires a dopaminergic-mediated gating signal. As a consequence, the carriers of the Val allele of COMT should be less efficient in the use of proactive control and recruit more extensively the lateral prefrontal cortex to obtain the same performance as the Met allele carriers.

As in our previous study (Grandjean, et al., 2012), when analyses were performed on the whole sample of participants, we observed no brain areas with sustained activity in the MI context requiring a proactive control strategy [see however Burgess and Braver (2010)]. Nevertheless, when sustained neural response was compared between the three genotype groups, increased brain activity in the left middle frontal gyrus was consistently observed in the carriers of the Val allele. We also observed decreased activity in anterior and mid-cingulate areas in these participants.

Activity in middle frontal and cingulate areas was previously observed, among a large fronto-parietal network, in studies exploring the neural substrates of interference using the Stroop task (Grandjean, et al., 2012; Laird, et al., 2005; Nee, et al., 2007; Roberts and Hall, 2008). Within that network, the DLPFC and ACC were associated with very specific role in conflict processing. For example, Botvinick et al. (2001; 2004) proposed that the ACC is involved in conflict detection and monitoring and will recruit the DLPFC when interference occurs in order to resolve conflict in a top-down manner by means of strategic adjustments in cognitive control. In order to select the appropriate response, the DLPFC would bias information processing in posterior brain regions (i.e., parietal cortex) to favor the most relevant criteria for performing the task.

As a whole, results obtained in the present study indicate, as previously suggested by Braver (Braver, 2012; Braver, et al., 2007) that the lower DA level in the carriers of the Val allele leads to a larger recruitment of the left middle frontal cortex, related to active maintenance of task goal in order to

perform the Stroop task efficiently in situations where proactive control is implemented. Moreover, we can also propose that this larger recruitment necessary to a correct performance could result from a less efficient involvement of the ACC in the Val allele carriers, this area being involved in the initial conflict detection and monitoring (Botvinick, et al., 2001; Botvinick, et al., 2004; Egner and Hirsch, 2005). Importantly, although several data [e.g. (Sharp, et al., 2010; Velanova, et al., 2008)] suggested the involvement of the cingulate cortex in cognitive processes associated with erroneous performance, it seems unlikely that the association we observed here between Val load allele effect and cingulate activity came from error-related activity, because only correct responses were used in the fMRI analyses. However, the number of errors committed by the participants in the different contexts was very low (from 2 to 10 %), precluding the exploration of this issue in a statistically meaningful way. Finally, we did not observe differential genotype-related transient activity in frontal regions for the processing of incongruent trials in the MI context (Grandjean, et al., 2012). These results also indirectly support the proposal that frontal dopamine level specifically influence the implementation of sustained, and not transient, brain activity during proactive control (Braver, 2012; Braver, et al., 2007).

4.2.The role of dopamine in the implementation of reactive cognitive control processes

According to the DMC model, the DA system does not influence reactive control processes. Here, we observed an effect of the Met allele mainly in the bilateral inferior frontal operculum, with a lower activity following the successful processing of interfering items occurring rarely (i.e., in the MC context). The inferior frontal operculum is classically associated with inhibitory processes (in a large range of tasks, for a review see (Collette, et al., 2006)), indicating more efficient transient inhibitory response in the carriers of the Met allele. A better inhibitory control in Met allele carriers by comparison to homozygous Val participants was also reported by Congdon (2009) with the stop-signal task, assessing motor response suppression.

Importantly, these results suggest that the dopamine level also influences the neural substrates related to reactive control processes. Indeed, it appears that most dopamine available will lead to a lowest recruitment of a set of brain areas including mainly the inferior frontal operculum, but also the right inferior frontal triangularis and the left superior frontal gyrus, when irrelevant information processing is successfully suppressed. These results are in line with those, presented just before, showing a more efficient sustained brain activity in Met allele carriers when the occurrence of interfering events is high. So, the purpose is now to understand how to explain that sustained brain activity in situation involving proactive control processes and transient brain activity in situation involving reactive control processes both benefit from a high dopamine level (i.e. greater benefit for Met than for Val carriers) in our task.

4.3.How to explain the positive effect of Met genotype loading on cognitive control?

To fully understand the effects of the COMT genotype on cognition, it may be necessary to consider whether a task requires tonic or phasic dopaminergic activation (Bilder, et al., 2004; Grace, et al., 2007). The tonic component is characterized by a constant, slow, irregular firing of DA neurons, whereas the phasic component is characterized by transient, high-amplitude activity, so-called burst firing. Bilder et al. (2004) hypothesize that Met and Val alleles of the COMT operate, respectively, to enhance the stability and plasticity of the neural network activation states that mediate the maintenance and updating of executive processes. More specifically, they suggest that (1) the Val allele, that decreases DA concentrations cortically, leads to a decreased stability of neural networks underlying task context representations, but there is also facilitation to switch or update network states mediating the resetting of working memory traces and flexibility in behavioral programs; (2) the Met allele, that increases DA concentrations cortically, increases the stability of networks mediating sustained task context representations, but makes it more difficult to switch or update the currently active networks associated with maintenance of task context.

Most of the tasks used to determine the effect of COMT genotype on executive abilities were multi-compound and thus influenced by both stability and plasticity functions [for example, successful performance on the n-back task requires both the maintenance of prior stimulus over time (stability) and their updating with more recent information (plasticity)]. These studies seem however to confirm that the Met genotype loading may confer greater stability in performance but seems disadvantageous when the task requires flexibility. Indeed, smaller switching costs (reflecting a higher level of cognitive flexibility) were observed in Val homozygous individuals (Colzato, et al., 2010) and reduced response time variability (reflecting greater stability in performance) was associated with Met loading (Stefanis, et al., 2005). Using a Stroop task, Rosa et al. (2010) found a Met advantage (in healthy and schizophrenic patients) for tasks requiring cognitive stability (reading the word) but no COMT effect when a moderate level of cognitive flexibility was required (naming the color) or when a conflict cost measure was calculated. Finally, de Frias et al. (2010) addressed the tonic-phasic hypothesis regarding the influence of COMT Val/Met genotype on cognition by using a mixed blocked/event-related fMRI design that enables the dissociation of sustained from transient brain activity during a 2-back working memory task. Although there were no differences in performance, Met carriers displayed a greater transient medial temporal lobe response in the updating phase of working memory (involving flexibility), whereas Val carriers showed a greater sustained PFC activation in the maintenance phase (requiring stability of process).

Our Stroop task requires interference resolution in contexts involving either stability of the naming process (MI context) or flexibility between reading and naming processes (MC context). This task appears thus particularly relevant to determine the influence of COMT polymorphism on tonic and phasic dopaminergic activation. In a statistical analysis evidencing sustained brain activity during proactive control (reflecting stability of cognitive process), we observed, in the carriers of the Val allele, increased brain activity in the left middle frontal gyrus, in association to decreased activity in cingulate areas. If increased sustained brain activity in the left middle frontal gyrus is clearly indicative of a disadvantage of the Val allele when the task condition requires stability of cognitive

processes, the decrease of activity in cingulate areas does not fit with the interpretation that less brain activity is indicative of more efficient cognitive processes. We nevertheless interpreted these results by suggesting that a lower stability in the process of conflict detection leads to the necessity of a larger recruitment of the areas related to the maintenance of task-goal representation (the left middle frontal gyrus). In agreement with that interpretation, Kerns et al. (2004) showed that the activity in the ACC for conflicting trials predicted subsequent PFC activity and adjustments in behavior.

However, we have no clear evidence for an advantage of the Val allele when the task requires flexibility of processes. Indeed, it could be inferred from the Dual Mechanism of Control account (Braver, et al., 2007) that the reactive control condition would be more dependent on phasic dopamine activation and consequently we would have expected that the Met carriers displayed a greater brain response in areas associated with conflict resolution when incongruent items were presented. We observed, on the contrary, a decreased activity in the frontal operculum that was interpreted as reflecting more efficient inhibitory processes. In the context of the optimal inverted-U-shaped dopamine level theory (Cools and D'Esposito, 2011; Cools and Robbins, 2004), one possible explanation could be that, even in cognitive context requiring flexibility of process (here, the processing of incongruent items in the MC condition) and thus phasic dopaminergic activity, the dopamine level of Val allele carriers remains too low to perform the task as efficiently as the Met allele carriers. Indeed, the inverted-U-shaped theory is based on results coming from the administration of dopaminergic drugs to groups of participants (Mattay, et al., 2003; Mehta, et al., 2000). We can argue that dopamine level in our groups is not sufficiently different to reverse the advantage of Met allele carrier's participants between the two conditions of the task. In agreement with that interpretation of a general too low dopamine level in Val allele carriers, we have observed a lower accuracy in the processing of incongruent items whatever the task context, suggesting less efficient inhibitory abilities in these participants, irrespective of the cognitive control required. Obviously, we cannot rule out the possibility that the phasic dopamine effect is very tenuous [see for

example (Rosa, et al., 2010)], that other genes than COMT are related to the phasic component of dopamine regulation [see for example (Bilder, et al., 2004)] or that our procedure was not perfectly designed to evidence the distinction between tonic/phasic dopaminergic regulation [for a clearer distinction between these two regulation systems see (de Frias, et al., 2010)].

5. Limitations of the study

One potential limitation to the behavioral part of our study is that our sample size (15 participants/group) is limited, although such a number of participants are usual and sufficient to observe significant effects in event-related fMRI designs. Indeed, it was previously showed that larger samples are necessary to evidence genetic effects on behavior than on brain functions (for a presentation of these studies, see (Mattay, et al., 2008)). This appears particularly true when very specific cognitive processes are under investigation (as discussed in the Introduction). Consequently, before concluding that the COMT genotype has no significant influence on the implementation of proactive cognitive control at the behavioral level, further investigations are needed in which the same kind of procedure to assess the involvement of proactive and reactive cognitive control processes will be administered to a large population (ideally up to 200-300 subjects) outside the fMRI environment.

6. Conclusion

As a whole, these results strongly suggest that, in the context of attentional control, variations in dopamine signaling mediated by COMT critically influence the implementation of sustained proactive control processes, as suggested by the DMC account (Braver, 2012; Braver, et al., 2007). Indeed, carriers of the Val allele need a larger recruitment of the left middle frontal cortex to actively maintain task goals necessary to correct performance. We related these results to lower tonic dopaminergic activation in these participants, reflecting stability of cognitive processes. However, contrary to our expectations based on the DMC model, our results indicate that the dopamine level also influence the neural substrates associated with reactive control processes, again with an

advantage for the carriers of the Met allele. This last result needs further investigation, notably to understand the relationships between reactive control and tonic/phasic dopaminergic activation supposed to reflect respectively stability and flexibility of cognitive control processes.

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Figures legends

Figure 1: Schematic representation of the task design. The upper part of the figure shows the general procedure for context presentation (a fixation cross was presented after every two or three blocks of stimuli) while the lowest part is devoted to the general procedure for item presentation (proportion of incongruent, congruent and neutral item is function of the block context). The letters B, N, V, R are the first letters, in French vocabulary, of the four possibilities of response [B = Blue; N = Black, V = Green, R = Red].

Figure 2: Behavioral results. (A) Mean median reaction times (ms) for the whole sample of participants in the MI, MC and MN contexts for incongruent (II), congruent (CI) and neutral (NI) items. (B) Mean accuracy (%) in MM, VM and VV groups for incongruent (II) and neutral (NI) items in the whole task. Error bars represent standard deviations.

Figure 3: Brain areas associated with proactive control in carriers of COMT Val and Met Allele. Areas showing increased brain activity in the anterior (**A**) and mid- (**B**) cingulate cortex in the MI (by comparison to MC) context for the Met allele carriers participants; and in the mid frontal gyrus **(C)** in the MI (by comparison to MC) context for the Val allele carriers participants. The regions are displayed on an individual participant structural image normalized on MNI standard. See Table 3 for coordinates. (ACC, anterior cingulate cortex; M. cing., mid-cingulate; MFg, middle frontal gyrus; MM = Met/Met participants; VM = Val/Met participants; VV = Val/Val participants).

Figure 4: Brain areas associated with reactive control in carriers of COMT Val and Met alleles. Areas showing increased brain activity in VV homozygous participants for incongruent items in the mostly congruent context by comparison to heterozygote VM and homozygous MM. **Top**: left and right inferior frontal operculum; **Bottom left**: superior frontal gyrus; **Bottom right**: inferior frontal gyrus triangularis. The regions are displayed on individual participant structural image normalized on MNI standard. See Table 5 for coordinates. (IFop, inferior frontal operculum; IFtr, inferior frontal

triangularis; SFg, superior frontal gyrus; MM = Met/Met participants; VM = Val/Met participants; VV = Val/Val participants).

Table 1. Demographic variables. Mean (standard deviation) for age and intelligence level (Raven's advanced progressive matrices test), number of males and females in each group.

	Val/Val (N=15)	**Val/Met (N=15)**	**Met/Met (N=15)**
Age	21.13 (2.33)	22.30 (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

Table 2. Sustained brain activity during proactive control - Group differences. Local maxima of brain regions showing more activation for incongruent, congruent and neutral items in the mostly incongruent condition than in the mostly congruent condition at a voxel p value < .001 uncorrected.

Hemisphere	Anatomical region	MNI coordinates			Cluster size	Z score	P value
		x	y	z			
MM > VV							
R	Anterior cingulate	12	46	0	40	3.84	< .0001
		4	28	14	38	3.63	< .0001
		0	40	22	52	3.67	< .0001
R	Mid cingulate	2	-16	30	58	3.40	<.0001
VV > MM							
L	Middle frontal gyrus	-30	6	44	10	3.48	<.0001
VM > MM							
L	Middle frontal gyrus	-30	8	42	14	3.55	<.0001
L	Inferior frontal triangularis	-42	16	26	68	3.69	< .0001
VM > VV							
R	Anterior cingulate	12	46	0	1175	4.71	< .0001*
		6	28	14	1175	4.32	< .0001*
L	Mid cingulate	-4	-38	36	44	4.15	< .001
		-2	-34	44	44	3.26	<.0001
L and R	Medial /superior frontal gyrus	-10	54	6	1175	4.24	<.0001
		-20	22	38	399	4.32	<.0001*
		-16	26	44	399	3.40	<.0001
		-6	36	48	399	3.86	<.0001
		20	50	16	64	3.69	<.0001
R	Middle frontal	24	32	32	49	3.69	<.0001
L	Inferior / orbital frontal gyrus	-40	38	-12	31	3.64	<.0001
VV>VM NOTHING							
MM > VM NOTHING							

L/R = left or right; x, y, z: coordinates (mm) in the stereotactic space defined by the Montreal Neurological Institute (MNI). * = significant at p<0.05 corrected.

Table 3. Sustained brain activity during proactive control – Specificity of the VAL vs. MET allele. Local maxima of brain regions showing more activation for incongruent, congruent and neutral items in the mostly incongruent condition than in the mostly congruent condition at a voxel p value < .001 uncorrected.

Hemisphere	Anatomical region	MNI coordinates			Cluster size	Z score	P value
		x	y	z			
MM and VM > VV							
R	Anterior cingulate	12	46	0	1264	4.77	< .0001*
		6	28	14	1264	4.43	< .0001*
R and L	Mid cingulate	0	-18	40	96	3.55	<.0001
		4	-16	32	96	3.40	<.0001
		-8	-38	34	46	4.43	<.0001
L	Medial superior frontal gyrus	-6	46	26	1264	3.93	< .0001
		-14	26	46	204	3.22	<.001
		-6	36	50	204	3.93	<.0001
		-6	26	56	204	3.49	<.0001
R	Middle frontal gyrus	24	32	32	30	3.55	< .0001
L	Inferior/orbital frontal gyrus	-42	38	-10	38	3.85	<.0001
VV and VM > MM							
L	Middle frontal gyrus (BA 6)	-30	8	42	22	3.88	< .0001
MM and VM < VV NOTHING							
VV and VM < MM NOTHING							

L/R = left or right; x, y, z: coordinates (mm) in the stereotactic space defined by the Montreal Neurological Institute (MNI). * = significant at p<0.05 corrected

Table 4. Transient brain activity during reactive control - Group differences. Local maxima of brain regions showing more activity for incongruent than neutral items in the mostly congruent condition at a voxel p value < .001 uncorrected.

Hemisphere	Anatomical region	MNI coordinates			Cluster size	Z score	P value
		x	y	z			
VV > MM							
R	Inferior frontal operculum	54	10	-2	219	3.70	< .0001
		58	4	2	219	3.55	< .0001
		60	-4	10	219	3.95	< .0001
VV > VM							
L and R	Inferior frontal operculum	-56	2	6	34	3.95	< .0001
		54	16	-2	60	3.90	< .0001
MM> VM, MM > VV & VM > VV VM>MM NOTHING							

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

Table 5. Transient brain activity during reactive control – Specificity of the VAL vs. MET allele. Local maxima of brain regions showing more activity for incongruent than neutral items in the mostly congruent condition at a voxel p value < .001 uncorrected.

Hemisphere	Anatomical region	MNI coordinates			Cluster size	Z score	P value
		x	y	z			
VV and VM > MM							
R	Anterior cingulate	12	6	40	20	3.43	< .0001
L	Mid cingulum	-14	-26	46	17	3.68	< .0001
R	Inferior frontal operculum	64	-4	8	29	3.45	<.0001
VV > MM and VM							
R and L	Inferior frontal operculum	54	12	-2	219	3.99	< .0001
		58	6	2	219	3.55	<.0001
		58	-4	8	219	3.76	<.0001
		-56	0	6	64	3.39	<.0001
R	Inferior frontal triangularis	50	34	-2	22	3.37	<.0001
L	Superior Frontal	-24	-6	58	16	3.20	<.001
MM and VM< VV, VV and VM < MM NOTHING							

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

Figure 1.

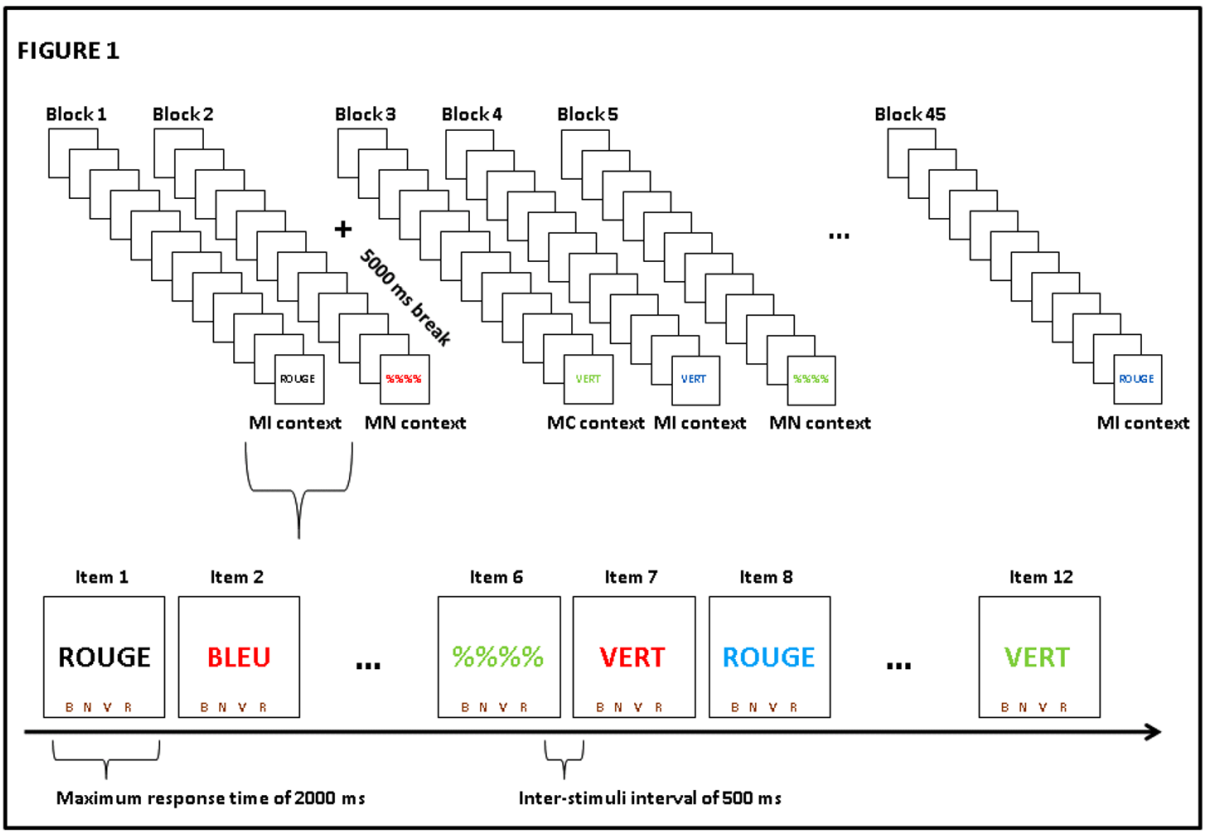


FIGURE 1
Block 1
Block 2
Block 3
Block 4
Block 5
Block 45
5000 ms break
ROUGE
%%%%
VERT
VERT
%%%%
ROUGE
MI context
MN context
MC context
MI context
MN context
MI context
Item 1
Item 2
Item 6
Item 7
Item 8
Item 12
ROUGE
BLEU
%%%%
VERT
ROUGE
VERT
B N V R
Maximum response time of 2000 ms
Inter-stimuli interval of 500 ms

Figure 2.

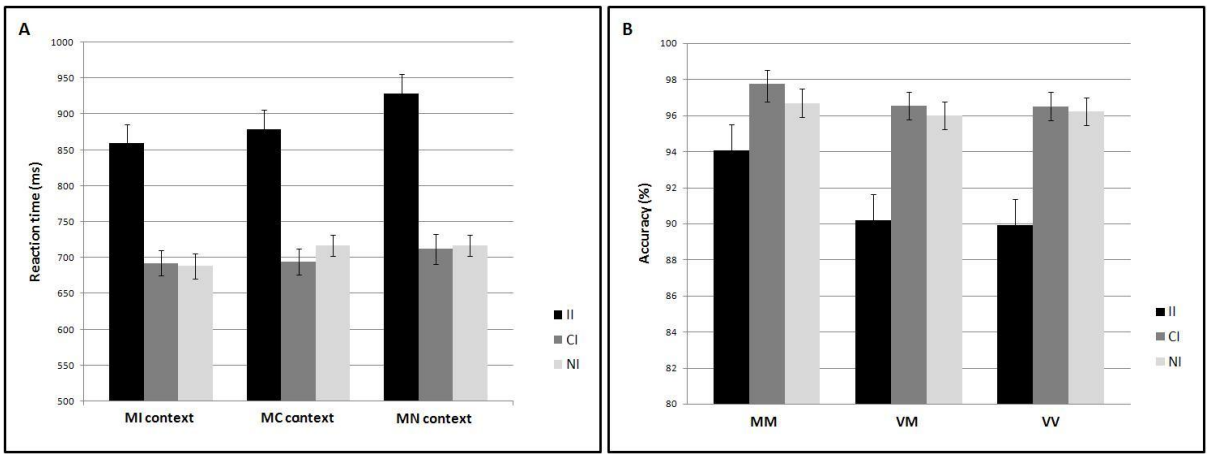

A
Reaction time (ms)
1000
950
900
850
800
750
700
650
600
550
500
MI context
MC context
MN context
II
CI
NI
B
Accuracy (%)
100
98
96
94
92
90
88
86
84
82
80
MM
VM
VV
II
CI
NI

Figure 3.

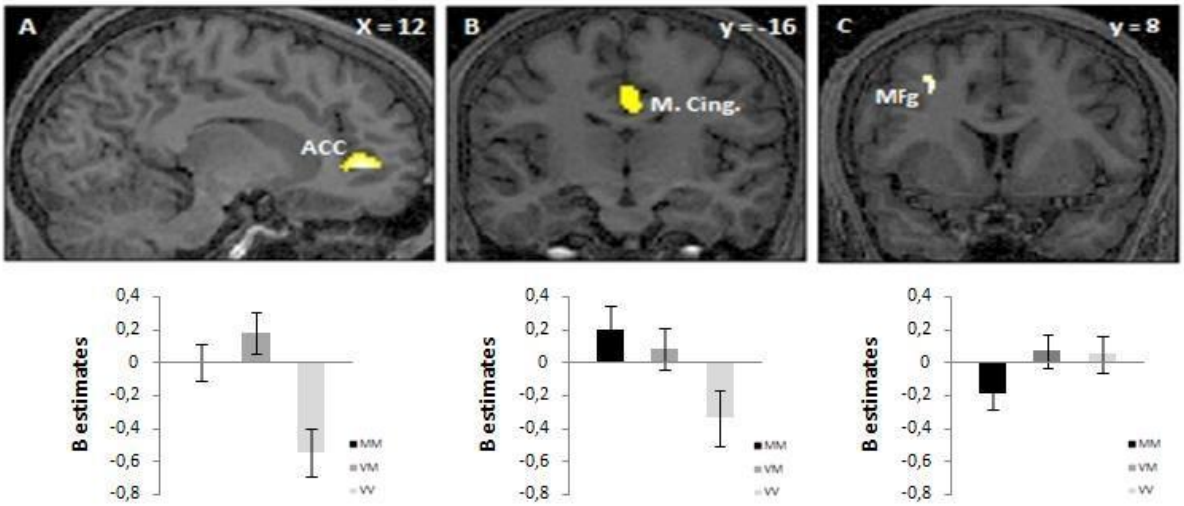
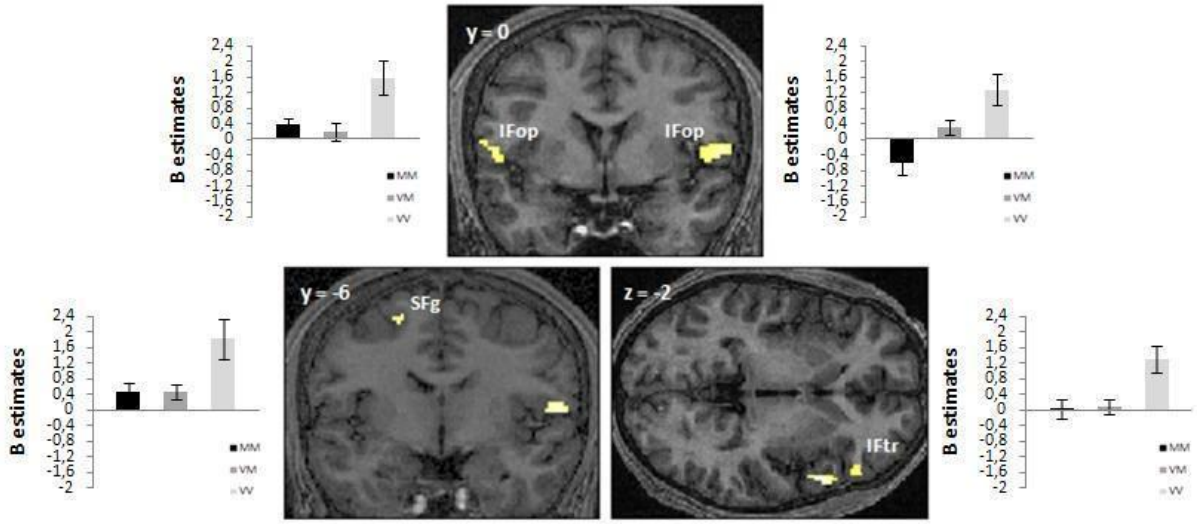

A
X = 12
ACC
B
y = -16
M. Cing.
C
y = 8
MFg
B estimates
0,4
0,2
0
-0,2
-0,4
-0,6
-0,8
MM
VM
VV

Figure 4.


y = 0
IFop
IFop
B estimates
2,4
2
1,6
1,2
0,8
0,4
0
-0,4
-0,8
-1,2
-1,6
-2
MM
VM
VV
y = -6
SFg
z = -2
IFtr