MODULATING EFFECT OF COMT GENOTYPE ON THE BRAIN REGIONS UNDERLYING PROACTIVE CONTROL PROCESS

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INTRODUCTION

Catechol-O-Methyltransferase (COMT) is an important enzyme which degrades catecholamines, such dopamine (DA), notably in the prefrontal cortex (PFC) [1]. The COMT gene is characterized by three genotypes, each associated with different COMT enzymatic activity. Precisely, individuals homozygous for met allele (MM) exhibit the lowest enzymatic activity, while homozygous for val allele (VV) have the highest. Heterozygotes (VM) exhibit an intermediate level of activity [2].

Given that interference resolution has been consistently associated with a large fronto-parietal network [3-4], and according that the effect of COMT genotype on executive functioning appears clearly associated to a similar brain network [5-7], we are interested to characterize the influence of COMT val158met genotype on the brain responses specifically associated to a condition of high interference requiring proactive control by opposition to a situation of low interference inducing reactive control.

METHODS

Forty-five right-handed French speakers young adults, aged from 18 to 30, were recruited and separated into **three groups** according to their COMT genotype : 15 VV (5 males), 15 MM (7 males) and 15 VM (8 males).

A modified form of the Stroop task [8] was administered in a fMRI session. The Stroop paradigm consists in the inhibition of a predominant response (WORD READING) to promote another one (COLOR NAMING).

Three kinds of items

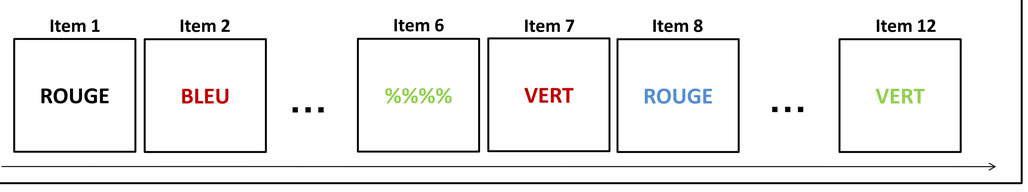
BLUE	RED	%%%%
Interfering Items (**II**)	Facilitator/congruent Items (**CI**)	Neutral Items (**NI**)

Three kinds of contexts (15 blocks of 12 items by context)

8II – 2CI – 2NI	**8CI – 2II – 2NI**	**8NI – 2II – 2CI**
Mostly incongruent context (MI)	Mostly congruent context (MC)	Mostly neutral context (MN)

=> Proactive control was implemented by MI blocks and reactive control by MC blocks.

Task : To name the ink color as fast and accurately as possible by pressing the corresponding key-response at the bottom of the screen.



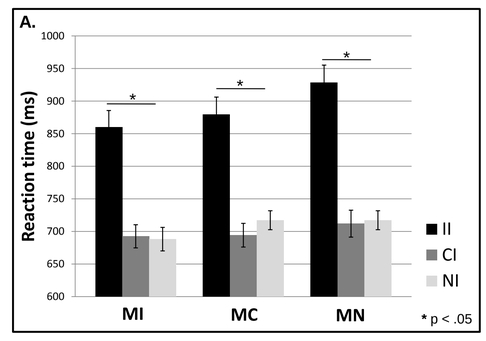
Brain imaging data were acquired on a 3T head-only scanner. Multislice T2*-weighted functional images were acquired with a gradient-echo echo-planar imaging sequence using axial slice orientation and covering the whole brain (32 slices, FoV = 220x220 mm², voxel size 3.4x3.4x3 mm³, 30% interslice gap, matrix size 64x64x32, TR = 2130 ms, TE = 40 ms, FA = 90°). Structural images were obtained using a high resolution T1-weighted sequence (3D MDEFT [9] ; TR = 7.92 ms, TE = 2.4 ms, TI = 910 ms, FA = 15°, FoV = 256 x 224 x 176 mm³, 1 mm isotropic spatial resolution).

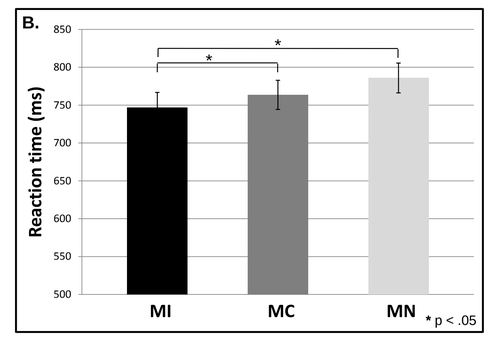
Preprocessing and statistical analyses were performed using SPM8 software. A 2-step analysis accounting for fixed and random effects was performed. At the first level (fixed effect analysis), the hemodynamic response specifically associated to proactive control by comparison to reactive control process was computed for each subject by contrasting the mostly incongruent blocks with the mostly congruent blocks (MI-MC). At the second level (random effect analysis), brain areas specifically associated to the same contrast were compared between groups using t-tests.

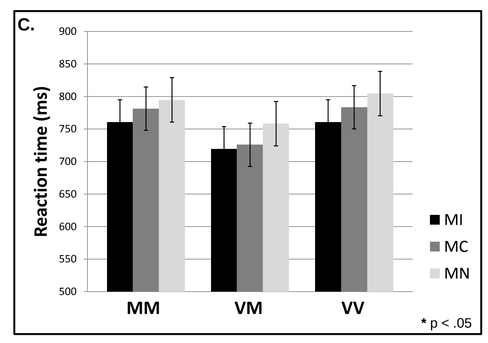
RESULTS

BEHAVIORAL RESULTS

ANOVA 3(groups) x 3(contexts) x 3(items): (A)Significant interference effect in the three contexts ; (B) Significant effect of context ; (C) No group effect on context or interaction.





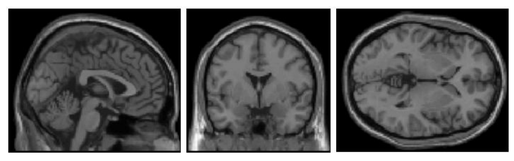


FIGURES : (A) Median reaction time (ms) in each context (MI - MC - MN) for interferent (II), facilitator (CI) and neutral (NI) items ; **(B)** Median reaction time (ms) for all item in the three contexts (MI - MC - MN) ; **(C)** Median reaction time (ms) in each group for mostly incongruent (MI), congruent (MC) and neutral (MN) contexts.

The same results were obtained with the analysis of responses accuracy.

fMRI RESULTS

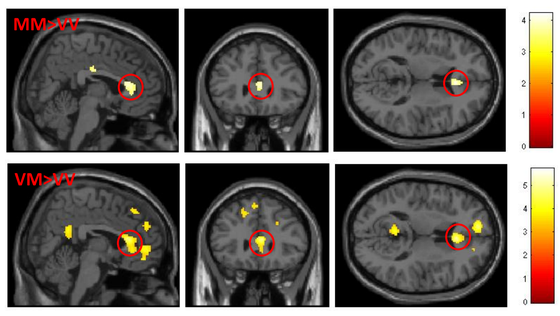
1. Main context effect : No significant difference in brain activity during MI by comparison to MC context (MI-MC).

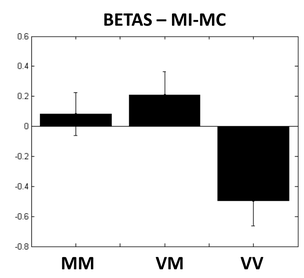


Statistical Parametric Mapping of differences between proactive and reactive strategies (MI-MC) in the three groups of subjects. Functional results are displayed at $P_{uncorrected} < .001$ over the normalized structural image of a typical subject.

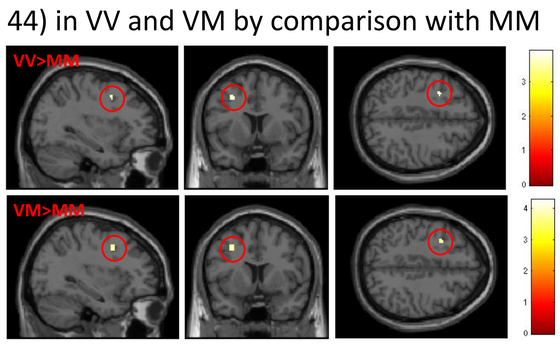
2. Group comparisons using t-test : (MI-MC at $P_{uncorrected} < .001$)

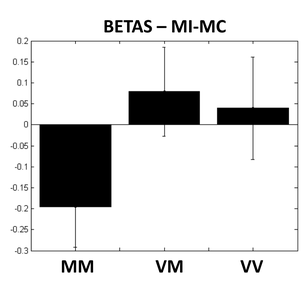
2.1. Increased brain activity in the anterior cingulate cortex (ACC : x = 4 ; y = 28 ; z = 12) in MM and VM by comparison with VV.





2.2. Increased brain activity in the middle frontal gyrus (MFg : x = -32 ; y = 8 ; z = 44) in VV and VM by comparison with MM





DISCUSSION

Our results show differential brain activity according to the COMT Val158Met genotype when subjects are engaged in proactive control process by comparison to reactive control process. Indeed, although there exists no behavioral group differences in the implementation of these two kinds of control processes, we observed a higher activity in the MFg for carriers of val allele and a higher activity in the ACC for carriers of the met allele.

These observations indicate that a lower DA level, as observed in the carriers of val allele, leads to a larger recruitment of brain areas associated to active maintenance of task goal [10] in order to perform the Stroop task efficiently in situation where proactive control is implemented. This could result from a less efficient involvement of the ACC, an area linked to conflict monitoring [10], in the chief of val allele carriers.

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