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Modulating effect of COMT genotype on the brain regions underlying inhibition

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INTRODUCTION

Catechol-O-Methyltransferase (COMT) is an important enzyme which degrades catecholamines, such dopamine, notably in prefrontal cortex (Männistö & Kaakkola, 1999). The COMT gene is located in the chromosome 22q11. A transition of guanine to adenine at codon 158 of this COMT gene results in a valine to methionine substitution (Lotta & al., 1995). This phenomenon leads to different COMT 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 higher. Heterozygotes (VM) exhibit an intermediate level of activity (Weinshilboum & al., 1999). A large number of studies reported a behavioral effect of COMT on executive functioning. However, most of them used multi-determined executive tasks (Barnett & al., 2007).

In this context, given the established role of frontal area in executive functioning, notably in inhibition (Nee & al., 2007; Laird & al., 2005), we were interested to determine the effect of COMT Val158Met genotype on activity in these areas when a task assessing a specific inhibitory process was administered.

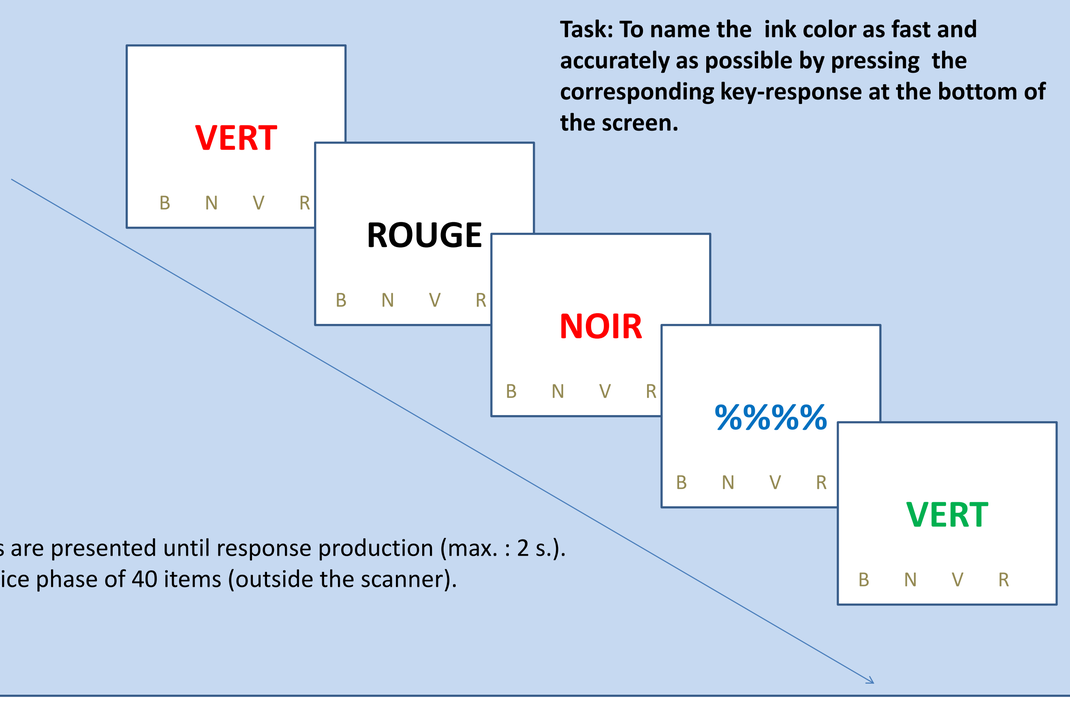
MATERIALS & METHODS

Forty-five right-handed native French speakers young adults, aged from 18 to 30, were recruited and separated into three groups according to their COMT genotype : 15 VV (6 males), 15 MM (7 males) and 15 VM (8 males).

A modified form of the Stroop task (Stroop, 1935) 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 :

BLEU	ROUGE	%%%%
Interfering item (II)	Facilitator item (IC)	Neutral item (IN)



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

Items are presented until response production (max. : 2 s.).
Practice phase of 40 items (outside the scanner).

Behavioral data analyses were performed with a factorial ANOVA 3 (group: VV, MM, VM) x 2 (item: interferent [II], neutral [IN]) using Statistica software.

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 mm^2, voxel size 3.4x3.4x3 mm^3, 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 [Deichmann & 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).

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 associated to the interference effect was computed for each subject by contrasting interferent and neutral items (I-N). At the second level (random effect analysis), brain areas associated to the interference effect were compared between groups using *t*-tests.

BEHAVIORAL RESULTS

ANOVA 3 (group) x 2 (item) : Significant interference effect in the three groups ; no group effect or interaction were observed.

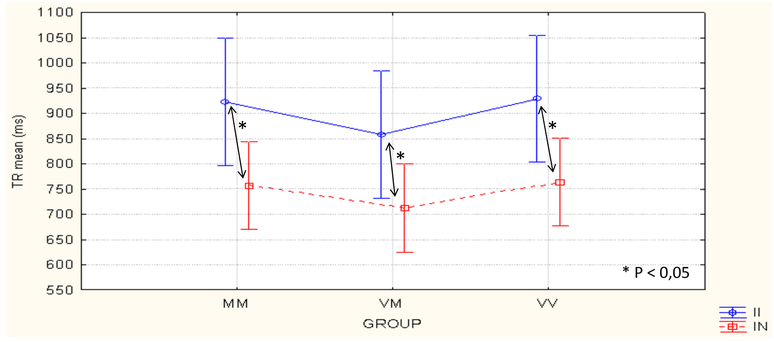


Figure 1 : Mean reaction time (ms) in each group (VV – MM – VM) for interferent (II) and neutral (IN) items.

fMRI RESULTS

1. Main task effect : Classical fronto-parietal network associated with interference resolution in the Stroop task.

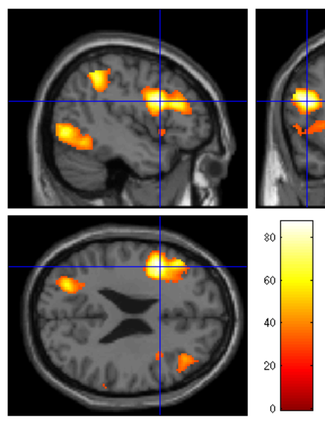


Figure 2 : Statistical Parametric Mapping associated with the interference effect (II – IN) in the three groups of subjects. Functional results are displayed at p_{FWE} < 0,05, over the normalized structural image of a typical subject.

2. Group comparisons using *t*-test : Increased brain activity in the superior temporal gyrus (x = -60; y = -52; z = 14) in VV and VM by comparison with MM.

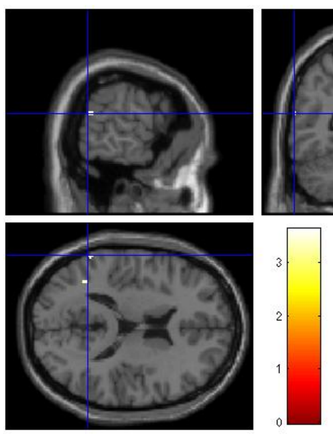


Figure 3 : Interference effect (II-IN): VV>MM ($P_{uncorrected}$ < 0,001).

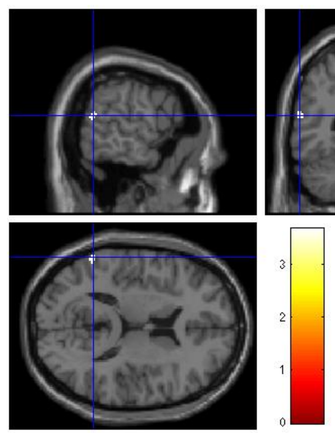


Figure 4 : Interference effect (II-IN): VM>MM ($P_{uncorrected}$ < 0,001).

DISCUSSION

The fronto-parietal brain network associated with interference resolution observed here in the three groups is consistent with prior reports (Nee & al., 2007; Laird & al., 2005).

Interestingly, similar interference effects are observed at a behavioral level in the three groups although as specific pattern of brain activity was found in the carriers of the val allele. Indeed, these subjects recruited supplementary areas in the superior temporal gyrus, an area previously observed in reading task and associated to phonological processes (Simos & al., 2000 ; Yagishita & al., 2008). This pattern of behavioral and brain imaging data seems to indicate that the reading process remains more activated in the VV and VM groups but not impede their inhibitory abilities in the Stroop task.

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