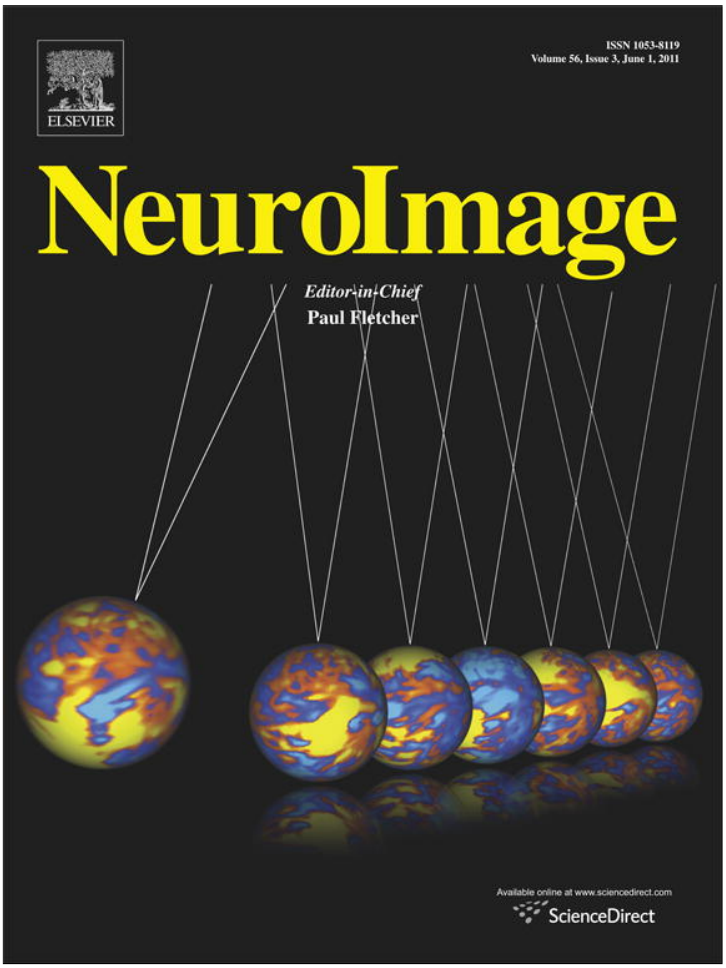

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# COMT and ANKK1 gene–gene interaction modulates contextual updating of mental representations

M. Garcia-Garcia [a,b,1], F. Barceló [c], I.C. Clemente [a], C. Escera [a,b,*]

[a] Institute for Brain, Cognition and Behavior (IR3C), University of Barcelona, P. Vall d'Hebron 171, 08035 Barcelona, Spain
[b] Cognitive Neuroscience Research Group, Department of Psychiatry and Clinical Psychobiology, University of Barcelona, P. Vall d'Hebron 171, 08035 Barcelona, Spain
[c] Clinical Neuropsychology Research Group, University of Balearic Islands, Ed. Beatriu de Pinos #12, Ctra. Valldemossa, km 7.5, E-07122 Palma de Mallorca, Spain

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ABSTRACT

The differential expression of the dopamine transmitter through its prefrontostriatal pathway has been proposed to account for individual differences in the updating of higher order task representations. Here we examined the interaction between two polymorphic variations of genes involved in the regulation of prefrontal and striatal dopamine (catechol-O-methyltransferase—COMT and ANKK1) on the neural mechanisms of task-set switching. A task-cueing paradigm was employed to measure behavioral costs and a scalp-recorded specific brain potential (novelty-P3) associated to distinct context updating operations in the face of either sensory or task novelty. The interaction between the COMT and ANKK1 genes was evidenced by corresponding specific behavioral costs and novelty-P3 amplitude enhancements reflecting task-set updating mechanisms. This effect was found only in individuals combining genes that yielded a balance between dopamine concentrations and receptor densities. Individuals displaying a putative "unbalance" showed enhanced novelty-P3 responses to all sensory changes, indicative of a task-set updating to sensory cues in a task-context independent fashion. These results support the epistasis of COMT and ANKK1 phenotypes in the flexible control of contextual information in humans.



## Introduction

The ability to flexibly adapt to constantly changing environmental demands requires selection and maintenance of appropriate–and suppression of inappropriate–mental representations for goal-directed behavior. This ability is dependent on the dopamine (DA) transmitter system (Cools, 2008; Kaplan and Oudeyer, 2007; DA Lewis et al., 2001; Lewis et al., 2003; Mehta et al., 2000; Sawaguchi and Goldman-Rakic, 1994). Indeed, DA-mediated activation of neurons in prefrontal cortex (PFC) facilitates stability of mental representations by inhibiting distracters (Durstewitz et al., 2000) whereas D2 receptor (DRD2) stimulation at the striatum facilitates the flexible update of the mental set by allowing new motivationally relevant representations (Frank, 2005). Therefore, the relationship between PFC DA concentrations and DRD2 density might lay beyond the widely accepted inverted-U model between DA transmission and updating operations in working memory, by which working memory updating is optimal within a limited range of DA transmission (Arnsten, 1998; Cools et al., 2004; Williams and Castner, 2006). Accordingly, the model proposed by Cools (2008) proposes that the updating of task-relevant contextual representations hinges on a subtle balance between the active maintenance of stable task representations and the flexible updating of those representations. Whereas the former function depends on PFC dopamine, the latter function has been proposed to depend on dopamine receptor stimulation in the striatum. There is controversy, however, about the mechanisms that determine an optimal DA concentration. Cognitive genetic studies have concluded that the balance between neurotransmitter concentrations and receptor density contributes to optimal working memory performance (Stelzel et al., 2009), provided that high DA concentrations would combine with higher receptor densities to lead to a context-dependent updating of working memory contents whereas low DA concentrations would be optimal with lower receptor densities.

Two well-known polymorphic variations involved in the regulation of PFC DA levels and DRD2 density might underpin such a model. For the *Val108/158Met* single nucleotide polymorphism (SNP) of the catechol-O-methyltransferase (COMT) gene (rs#4680; Lachman et al., 1996; GenBank accession number: AY341246), the substitution of Met by Val increases the efficiency of the enzyme (Mannisto and Kaakkola, 1999), which in turn inactivates DA diffused out of the synaptic cleft in the PFC (Bilder et al., 2004). On the other hand, the SNP *TaqIA* in the ankyrin repeat and protein kinase domain-containing 1 (ANKK1) gene (rs#1800497; GenBank accession number: AF050737) has been related to DRD2 expression, so that A1 allele carriers show a 30%–40% reduction in DRD2 density (Ritchie and Noble, 2003). According to this, individuals homozygous for Met and lacking the A1 allele (i.e., MetA1−) and those

* Corresponding author at: P. Vall d'Hebron 171, 08035 Barcelona, Spain. Fax: +34 934 021 584.
*E-mail address:* cescera@ub.edu (C. Escera).
[1] Currently at Phyllis Green and Randolph Cowen Institute for Pediatric Research, NYU Child Study Center, 215 Lexington Ave, 14th Floor, New York, NY 10016, USA.

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homozygous for Val and presenting the A1 allele (i.e., ValA1+) are expected to display a balance between PFC DA levels and DRD2 density. In contrast, individuals homozygous for Met and presenting the A1 allele (i.e., MetA1+) would display higher levels of PFC DA concentrations and low DRD2 density while those homozygous for Val and A2 (i.e., ValA1−) would be expected to display lower levels of PFC DA concentrations and high DRD2 density. Moreover, the inferred analysis of prolactin levels suggests that the former two groups display high DA concentrations while the latter and "unbalanced" groups display lower DA concentrations (Reuter et al., 2005). Consequently, ValA1− individuals with low PFC DA and high striatal DA expression will show both high distractibility and high flexibility. In turn, at the other end of this hypothetical continuum, MetA1+ individuals with high PFC DA and low striatal DA expression will hypothetically present with both high stability and low flexibility of task representations. From these premises, our prediction is that ValA1− would show a tendency to task-irrelevant distraction whereas MetA1+ individuals will show a tendency to task-relevant perseveration.

In the present study, we tested the hypothesis that individuals with a putative balance between prefrontal dopamine availability and D2 receptor density (i.e., MetA1− ValA1+) would show a more context-dependent updating of task-set information compared to individuals presenting either the lowest or the highest levels (i.e., ValA1−, MetA1+), and that this differentiation should be paralleled by the scalp-recorded novelty-P3 (nP3) response, a neural signature derived from the human electroencephalogram (EEG) associated with context updating operations in the face of both sensory (Escera et al., 1998; Escera et al., 2001; Escera and Corral, 2007) and task novelty (Barcelo et al., 2002; Barcelo et al., 2006). In order to do so, participants performed a task-cueing protocol inspired by the Wisconsin Card Sorting Test (WCST; Rubinstein et al., 2001) and adapted for measuring event-related brain potentials (ERPs; Barcelo, 2003). This protocol is designed to segregate the behavioral and brain responses to sensory changes from those related to the updating of higher order task-set information in working memory.

## Materials and methods

### Participants

Forty individuals (all Caucasian, 6 men, 2 left-handed, mean ± SD age; 22 ± 4.2 years, range 18–29 years) participated in the study. They were selected from a wider sample of volunteers in which the two genotypes of study were in Hardy–Weinberg equilibrium. All participants were interviewed through an adapted version of the Clinical Interview of the Diagnostic and Statistical Manual (DSM IV-R), for exclusion of subjects with neurological and psychiatric illness, phobias, and drug consumption. All participants gave informed consent at each phase of the experimental procedure (interview, buccal cells extraction and electroencephalographic–EEG–recordings) according to the Declaration of Helsinki and the Ethic Committee of the University of Barcelona. All subjects had normal or corrected-to-normal vision and normal audition. After exclusion by diagnostic criteria and following analyses of the *COMTVal108/158Met* and *ANKK1TaqIA* polymorphisms, participants homozygous for the *COMT* gene (Met/Met, Val/Val), and those presenting the most frequent alleles for *ANKK1* (A1, A2) were selected for an EEG recording session. Participants genotyped as Met/Met were assigned to the MetA1+ group when they presented the A1 allele (A1/A1 or A1/A2) and to the MetA1− group when they were homozygous for the A2 allele of the DRD2 gene. Participants genotyped as Val/Val were assigned to the ValA1+ group when they presented the A1 allele (A1/A1 or A1/A2) and to the ValA1− group when they were homozygous for the A2 allele for the DRD2 gene. Five participants were excluded from the analyses due to excessive artifacts in their EEG recordings. From the remaining 35 individuals, 6 composed the MetA1+ group, 9 the MetA1− group (3 men), 8 the ValA1+ group (2 men), and 12 were included in the ValA1− group (1 man). Participants from each of the genetic groups did not differ significantly in age, state or trait anxiety scores (STAI, Spielberger et al., 1983).

### DNA isolation and genotyping

DNA was collected with cheek cell swabs and extracted using the Epicentres® BuccalAmp™ DNA Extraction Kit (Epicentre, Madison, WS). Upon isolation of DNA, both single nucleotic polymorphisms (SNP) for the *COMTVal108/158Met* and *ANKK1TaqIA* genotyping were performed by real time PCR using fluorescence detection technique by means of the Applied Biosystems TaqMan technology (Applied Biosystems, Foster City, CA, USA).

### Procedure

A task-cueing protocol inspired by the WCST (Rubinstein et al., 2001) and adapted for measuring ERPs (Barcelo, 2003) was administered to participants. Each trial consisted of a tonal cue followed by a target display with 4 key cards on top of 1 choice card, all centered on a computer screen, and subtending a visual angle of 4º horizontally and 3.5º vertically. Subjects were instructed to match the choice card with 1 of the 4 key cards following 2 possible task rules (color or shape). Before target onset, 1 out of 4 tonal cues explicitly informed the subject whether to sort the card according to either 'color' (500/1000 Hz) or 'shape' (2000/4000 Hz) rules. Therefore, this design allowed for an independent manipulation of cue-switches, representing only a change in sensory stimulation, and task-switches, which requires a change in the task rules, and thus, an update of stimulus-response rules in WM (Barcelo et al., 2002; Barcelo et al., 2006). Three trial types were thus defined. In the repeat trials, both the tonal cue and the task were repeated relative to the previous trial. In the cue-switch trials, only the cue changed but the task remained the same as in the previous trial. In the task-switch trials both cue and task changed. The association of low (500/100 Hz) and high (2000/4000 Hz) tones to task rules was counterbalanced across participants. Binaural tones were delivered through Sehnheiser® HD202 headphones with a duration of 200 ms, 10 ms rise/fall times and 65 dB SPL. The meaning of the tonal cues was reversed for half of the subjects. All stimuli were presented with the stimulation program Presentation® (Neurobehavioral Systems Inc., Albany, CA). Responses were made using 4 keys on a keyboard, mapped onto the 4 fingers of the dominant hand, in an array corresponding to the layout of the 4 key-cards. All 3 trial types were randomly presented with the same overall probability along the 200 trials of the experimental block, as well as during the 50 practice trials. The cues related to each criterion were employed 5 times during the instruction period of the practice block to ensure that each participant had correctly learnt the cue-task association. The cue-target interval randomly varied between 650 ± 150 ms, thus, minimizing the effects of a constant preparation interval (Rogers and Monsell, 1995), and the target remained on the screen until a response was given (up to a maximal of 3000 ms). Response-cue intervals also varied randomly around 1100 ± 100 ms within the trial block.

### EEG data acquisition

Electroencephalographic activity was recorded (ANT Software b.v., Enschede, The Netherlands) during task performance from 64 scalp electrodes following the extended 10/10 convention in an electrically and acoustically shielded room. Horizontal and vertical electro-oculographic recordings were obtained with electrodes placed at the outer cantus of the right eye and above the right eye. The common reference electrode was placed on the tip of the nose, and the ground was located at the chest. The EEG was amplified and digitized at a sampling rate of 512 Hz. Impedances were kept below 10 kΩ during the whole experimental recording session, which lasted about 25 min.

*Data processing*

Brain potentials locked to the cue were extracted by averaging offline the response obtained for each trial type (repeat, cue-switch and task-switch), for an epoch of 800 ms including a pre-stimulus baseline of 200 ms. The first 5 trials of the block were excluded from analysis. Frequencies above 30 Hz were digitally filtered out from individual EEG epochs prior to brain potentials averaging. EOG correction was performed via a blind source separation technique with ASA 4.5 of ANT® Software (Enschede, The Netherlands; as described in Belouchrani et al., 1997). After EOG correction, any epochs containing EEG activity exceeding ± 100 μV peak-to-peak amplitudes were rejected from further analysis. The mean percentages of clean EEG epochs retained for brain potentials averages were 74.4% (about 50 trials), 75.1% (about 54 trials) and 72.7% (about 49 trials) epochs from the repeat, cue-switch and task-switch conditions, respectively, which did not differ between any of the trial types.

*Data analysis*

For behavioral analysis, any correct button press within 200–3000 ms after target onset was regarded as a hit, and the mean RT was computed for hit trials only. Hit rate and mean RT were submitted to a two-way mixed ANOVA with one repeated-measures factor (Trial type: repeat, cue-switch, task-switch), and two between-subject factor (COMT: Val and Met; ANKK1: A1+ and A1−). Pair-wise post hoc comparisons were performed to examine any significant difference between conditions.

For the analysis of brain responses, the fronto-central positive nP3 brain response was identified and measured as mean amplitudes in the latency window from 300 to 340 ms following the cue, at channels F3, F4, Fz, C3, C4, Cz, P3, P4 and Pz, for hit trials only. A three-factor repeated-measures ANOVA was performed on all these ERP measures including three within-subjects factors: Trial type (repeat, cue-switch and task-switch), Frontality (three levels for frontal, central and parietal channels) and Laterality (three levels for the left, middle and right channels), as well as the two between-subject factors COMT (Met and Val) and DRD2 (A1+ and A1−). Pair-wise post hoc comparisons were performed between all trial types to examine whether any specific effect was due to the updating of either sensory or task representations during cue-switching or task-switching, respectively. The Greenhouse–Geisser correction was applied to the degrees of freedom of the ANOVAs, and the corrected *P*-values were reported whenever it was appropriate. Target-locked brain potentials will not be reported here as they did not account for any group-related behavioral effects or interactions in the present study.

## Results

*Performance*

Mean accuracy was over 90%. All groups showed a decrease in accuracy following a tonal switch (main effect of Trial type: $F_{2,62}=33.0$, $p<0.001$), which was due to a decrease in hit rate in task-switch as compared to cue-switch trials ($F_{1,31}=41.23$, $p<0.001$; Fig. 1A). No effect of group was found for accuracy data. As for response times (RT), a main Trial type effect ($F_{2,62}=73.9$, $p<0.001$) was due to an increase in mean RTs from repeat to cue-switch trials ($F_{1,31}=73.5$, $p<0.001$), with no differences between cue-switch and task-switch trials. The four groups did not differ in their mean RTs. However, a Trial type × COMT × DRD2 interaction (i.e., including all 3 trials types; $F_{2,62}=3.6$, $p=0.036$) revealed larger mean RTs in task-switch as compared to cue-switch trials (Trial type × COMT × DRD2: $F_{1,31}=5.7$, $p=0.023$; when including only cue- and task-switch trials) for the ValA1+ ($F_{1,7}=3.7$, $p=0.097$) and Met A1− groups ($F_{1,8}=8.7$, $p=0.018$) only. In contrast, the ValA1− and MetA1+ groups did not show any significant difference in their mean RTs between cue-switch and task-switch trials (Fig. 1B). A post hoc *t*-test analysis comparing average RTs of task-switch minus repeat trials revealed larger RTs for ValA1− relative to MetA1+ ($p=0.046$).

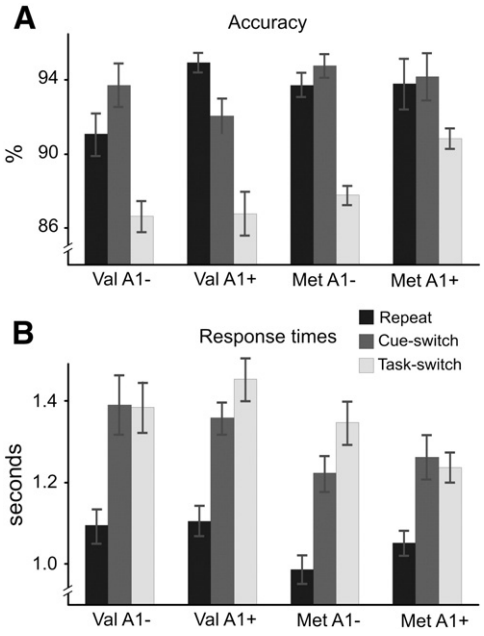


**Fig. 1.** A) Accuracy for all three trial types in all four groups. Accuracy decreased in task-switch relative to cue-switch trials in all groups similarly. B) Response times for all three trial types in the four groups. All groups showed an increase in RT for cue-switch compared to repeat trials. However, ValA1+ and MetA1− groups showed an increase in task-switch as compared to cue-switch trials whereas ValA1− and MetA1+ reached already their largest RT in cue-switch trials with no further increase in task-switch trials.

*Novelty-P3 brain potential*

A specific increase in the amplitude of the fronto-central nP3 positivity to tonal cues (main Trial type effect: $F_{2,62}=11.9$, $p<0.001$) was observed both in response to cue-switch relative to repeat tones ($F_{1,31}=7.5$, $p<0.001$), and in response to task-switch relative to cue-switch tones ($F_{1,31}=6.3$, $p=0.017$). Remarkably, a significant Trial type × COMT × DRD2 interaction (including all 3 trial types; $F_{2,62}=3.9$, $p=0.029$) revealed larger mean nP3 amplitude to task-switch tones as compared to cue-switch tones (Trial type × COMT × DRD2: $F_{1,31}=7.5$, $p=0.010$; when including only cue- and task-switch trials) in ValA1+ ($F_{1,7}=17.3$, $p=0.004$) and MetA1− individuals ($F_{1,8}=6.8$, $p=0.031$). In contrast, ValA1− and MetA1+ groups showed similar mean nP3 amplitudes to cue-switch and task-switch tones, but larger nP3 amplitudes to cue-switch relative to repeat tones (Trial type × COMT × DRD2: $F_{1,31}=4.8$, $p=0.036$; Fig. 2A, B).

## Discussion

The present study explored the role of a gene–gene interaction related to DA regulation, namely *COMTVal108/158Met* and *ANKK1TaqAI*, on the neural correlates of the updating of contextual information. Although all groups experienced an increase in mean RT following a sensory change, only ValA1+ and MetA1− individuals also revealed a context-dependent and task-specific switch cost, showing longer mean RTs when confronted with sensory changes that also demanded a change in higher-order task representations (Fig. 3A). In contrast, the ValA1− and MetA1+ groups showed comparable mean RTs in cue-switch and task-switch trials. Interestingly, only ValA1+ and MetA1− individuals displayed increased amplitudes in the brain signature for

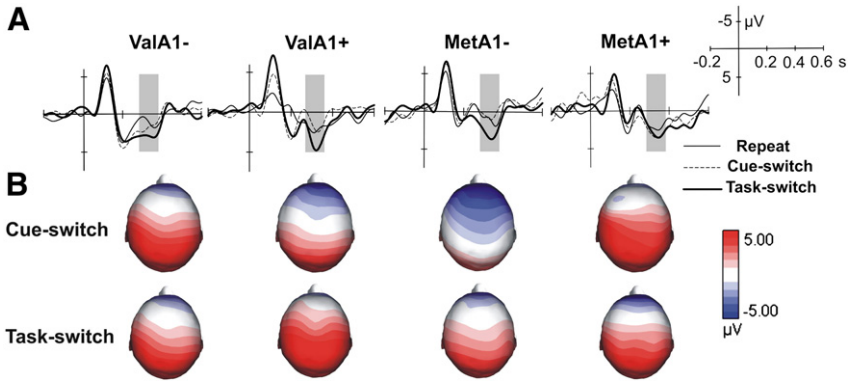


**Fig. 2.** A) Brain potentials for all three trial types in the four groups. The nP3 potential (shadowed) showed larger amplitudes in cue-switch relative to repeat trials in ValA1− and MetA1+ groups but appeared with similar amplitude for cue-switch and task-switch trials. In contrast, ValA1+ and MetA1− displayed similar amplitudes for repeat and cue-switch trials, but larger amplitudes in task-switch compared to cue switch trials. B) Scalp distribution of the nP3 brain potential for cue-switch trials and task-switch trials for all four groups. ValA1− and MetA1+ display a parietally distributed increase of the brain response in task-switch relative to cue-switch trials.

updating contextual information in task switch as compared to cue switch trials, although similar amplitudes were observed in repeat and cue-switch trials. In turn, ValA1− and MetA1+ groups showed increased nP3 amplitudes to cue-switch as compared to repeat trials, but no differences between cue-switch and task-switch trials. These results suggest that individuals with a balance between PFC DA levels and DRD2 density (i.e., ValA1+, MetA1−; that is, those individuals that are neither extremely flexible–or distractible–nor extremely stable or rigid) are those who show the most common patterns of context-dependent updating of information according to the ongoing task situation (Fig. 3B).

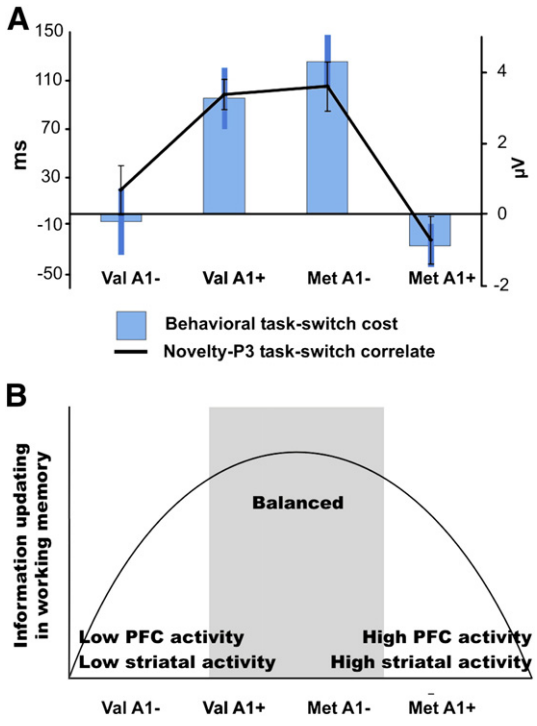


**Fig. 3.** A) Behavioral costs and nP3 brain potential amplitude increases in task-switch compared to cue-switch. The bars show RT in task-switch trials minus RT in cue-switch trials for all four groups. The lines plot the mean amplitude of the nP3 at Cz channel for task-switch trials minus amplitudes in cue-switch trials for all four groups. Notice that the behavioral RT costs displayed by the ValA1+ and MetA1− groups are paralleled by the modulation of the nP3; in contrast, no behavioral RT costs for task-set reconfiguration was observed in ValA1− and MetA1+ groups, as well as no modulation of the nP3 became evident. B) Inverted-U model of PFC DA activity resumed by Williams and Castner (2006). The four groups combining polymorphisms for the COMT and ANKK1 are disposed along the *X*-axis according to the balance between PFC DA concentrations and DRD2 density. The multifaceted role of DA activity accounts for the efficient manipulation of information in working memory through an inverted-U function, whereby "balanced" levels of prefrontal DA and DRD2 density (shadowed) results in optimal working memory performance whereas "unbalanced" PFC DA concentrations and DRD2 density leads to suboptimal manipulation of information in working memory. Remarkably, the results obtained in the present study and summarized in Fig. 2C fit the proposed inverted-U model of PFC DA activity and contextually efficient updating of information.

A crucial role of PFC in cognitive control consists of making the necessary adjustments in attentional bias in the face of ongoing environmental demands (Brass et al., 2005). This crucial function involves the DA system (Cools, 2008; Garcia-Garcia et al., 2010a; Garcia-Garcia et al., 2010b; Kaplan and Oudeyer, 2007; DA Lewis et al., 2001; Mehta et al., 2000; Sawaguchi and Goldman-Rakic, 1994) putatively through a reciprocal relationship between PFC and striatal DA (Akil et al., 2003; Meyer-Lindenberg et al., 2002). This interplay is thought to regulate the stability and flexibility of mental representations, maybe through the modulation of the firing of prefrontal pyramidal neurons, which is enhanced during maintenance in the delay period of a memory task (Durstewitz et al., 2000) and is modulated by the DA neurotransmitter through stimulation of D1 receptors at the PFC (Durstewitz et al., 2000; Durstewitz and Seamans, 2002; Sawaguchi and Goldman-Rakic, 1994). Hence, we might approach the role of PFC DA on the updating of task-representations by examining the effect of genes regulating PFC DA levels and DRD2 density on the updating of sensory and task information in working memory. *COMTVal* homozygous individuals are expected to have decreased PFC DA concentrations relative to *Met* homozygous individuals, and consequently, the former are expected to sustain comparatively less stable task-set representations (Bilder et al., 2004; Winterer et al., 2004). On the other hand, *ANKK1TaqIA A1* carriers show a 30%–40% reduction in DRD2 density (Ritchie and Noble, 2003) as compared to *A2* homozygous individuals as shown by in vitro and in vivo studies (Jonsson et al., 1999; Pohjalainen et al., 1998), and display thus lower D2 receptor binding (Thompson et al., 1997), which has been related with comparatively less efficient updating of newly relevant task-set representations (Cools, 2008). Therefore, a balance between neurotransmitter concentrations and DRD2 density might account for the optimal balance between cognitive stability and flexibility for updating operations in working memory in a context-dependent fashion.

Interestingly, the observation of largest behavioral RT costs following any change in acoustic stimulation without any further increase in RT costs for task-switch trials in individuals with the putative "unbalance" between DA concentrations and DRD2 density (i.e., ValA1− and MetA1+) suggests that these groups reconfigured the current task-set following any tonal change and irrespective of the ongoing task context.

A closer look at the behavioral data reveals that the reasons why the "unbalanced" groups did not show a task-switch cost seem to differ between the ValA1− and the MetA1+ groups. Thus, the ValA1− group seemed more distractible toward irrelevant cues and showed larger cue-switch costs (thus, reducing the task-switch cost) than MetA1+ individuals, which is consistent with Cools' (2008) hypothesis about the interaction between PFC and striatal DA for regulating two different dimensions of cognitive control: flexibility and stability of mental representations, placing this group at the most flexible but distractible extreme of the four analyzed groups. Differently, individuals displaying a "balance" between DA concentrations and receptor density showed context-dependent behavioral correlates of the control of attention, consisting of sensory-specific RT costs related to the updating of perceptual representations during cue-switching, and also task-specific RT costs related to the updating of higher-order task-set representations (Fig. 3A, B). This behavioral pattern seems more adjusted to the expected context-dependent use of the attentional resources in the present task context, as they only resort to a high-level processing when it is required by the environmental context, in this case, the cue prompting for a switch in the sorting rule.

The epistasis between COMT and DRD2 genes has been previously shown behavioral benefits in the manipulation of working memory contents (Stelzel et al., 2009), and hence, a balance between DA concentrations and DRD2 density seems to facilitate a context-dependent updating of memory representations. Moreover, previous studies show larger interference in a Stroop task in the "balanced" groups (Reuter et al., 2005), inferred from prolactin levels analysis to display larger DA concentrations (Reuter et al., 2006). Therefore, in light of these results one could argue that those individuals with higher DA concentration show a switch cost as a consequence of integrating task rule information into working memory. However, they only rely on this extra time cost when it is actually required by the context while the other two groups show this cost every time a sensory change occurs. The combined effects of COMT activity and DRD2 density might thus reflect the interaction between a gating mechanism for the updating to new task-set representations, and another mechanism for the online maintenance of task representations promoted by PFC DA concentrations (Arnsten, 1998; Cools et al., 2004).

Because the nP3 response accounts for operations of context-updating involved in the processing of both sensory novelty (Escera et al., 1998; Escera et al., 2000; Escera and Corral, 2007), and task novelty (Barcelo et al., 2002; Barcelo et al., 2006), it has been established as a brain signature of the updating of contextual information (Barcelo et al., 2006; Barcelo et al., 2007; Perianez and Barcelo, 2009). The comparison between cue- and task-switch trial types allows us to examine the costs elicited by a change in sensory stimulation (cue-switch minus repeat trial types) and the switch costs elicited by a sensory change that is also accompanied by a change in higher-order task representations (the task rules; i.e., task-switch minus repeat trials). Therefore, our task design independently manipulated two types of updating operations in working memory by comparing these two different types of behavioral costs: task-switch versus cue-switch costs. In the two "unbalanced" groups, the amplitude of this brain nP3 brain potential was increased in cue-switch trials compared to repeat trials, although it did not differ between cue- and task-switch trials, in parallel with the observed behavioral switch costs. This electrophysiological pattern suggests that individuals in the "unbalanced" group process every sensory change regardless of its significance for switching or repeating the previous task-set. Accordingly, the behavioral results showed no dissociation between a change in acoustic stimulation accompanied by either a repetition or a switch in the sorting rule. Both the electrophysiological and the behavioral patterns suggest that these subjects reconfigure the higher-order task-set representation following every cue switch, and irrespective of its task relevance. Hence, we interpret that these individuals are updating WM representations (the sorting rule) in cue-switch and task-switch trials similarly, that is, after any sensory change, irrespective of the previous trials. They are performing a mental set switching (updating WM representations) in a fashion that is less adequate of the context. Therefore, Fig. 3B is showing behavior and brain measure of the updating of WM representations that might be interpreted as a signature of lower task-adequacy. A similar rigid updating of contextual information was reported by Stelzel et al. (2009), and could indicate a lesser capacity for integrating sensory changes into the ongoing task context. Reversely, individuals with genetically based "balanced" levels of PFC DA concentrations and DRD2 density showed similar nP3 amplitudes for repeat and cue-switch trials and an enhanced nP3 brain potential in task-switch relative to cue-switch trials. They also displayed larger RTs when an update of task representations was required (task- versus cue-switch trials). These response patterns indicate task-specific context-dependent updating of task-set information (Fig. 3A, B). It is interesting to note that, nevertheless, MetA1+ individuals showed the fastest RTs of all groups with no significant trade-off in accuracy. It remains unknown whether this faster–although not necessarily more flexible or adaptive–strategy would result in larger error rates under more demanding conditions.

Several clinical (Cools et al., 2001; Cools et al., 2003), phamachological (Mehta et al., 2000; Mehta et al., 2004) and animal studies (Crofts et al., 2001) have confirmed the involvement of the PFC—striatum DA system in cognitive control processes such as task-switching. DRD2 are known to be mostly expressed at human striatum (Camps et al., 1989). On the other hand, different data have implicated dysfunction of the anterior cingulated cortex (ACC) and the dorsolateral PFC (dlPFC; prefrontal regions where COMT is mostly expressed; Bilder et al., 2004) along with the striatum as contributing to the pathophysiologic mechanisms of attention deficit hyperactivity disorder (ADHD; Bush et al., 2005; Durston et al., 2003), known to show a poor ability to flexibly adjust behavior to environmental changes (Nigg and Casey, 2005). Indeed, ACC activation is altered in ADHD patients (Makris et al., 2010) whose pharmacological target is the striatal DA system (Volkow et al., 2001). The ACC, area associated to novelty detection (Bush et al., 2008; Weible et al., 2009), has been found as a generator of the nP3 brain potential (Dien et al., 2003), and both ACC and dlPFC show an enhancement in their BOLD signal in paradigms eliciting the nP3 (Huang et al., 2005). The nP3 brain potential seems, thus, a trustable endophenotype for mapping gene risk for attentional dysfunctions. Indeed, the impoverished behavior observed in patients with dysfunction in the striatum, such as impairments in the WCST and other task-switching analogues associated to Parkinson's disease (Cools et al., 2001; Cools et al., 2003; Cools et al., 2004; Cools et al., 2006; Cools, 2008; Meiran et al., 2004), have been attributed to a deficit in the flexible use of abstract rules (Meiran et al., 2004; Yehene et al., 2008). Likewise, the aforementioned ADHD has been related to a poor ability to flexibly adjust behavior to environmental changes (Nigg and Casey, 2005), and has been treated pharmacologically by increasing striatal DA transmission in order to improve attentional functions (Volkow et al., 2001).

The finding revealing that the *ANKK1TaqIA* polymorphism actually lies 10 kb downstream of DRD2 gene, within a protein-coding region of the adjacent ankyrin repeat and protein kinase domain-containing 1 gene (Neville et al., 2004) has raised the question of how a mutation located 10 kb downstream of DRD2-coding gene may affect DRD2 expression. Strong linkage disequilibrium described between the *TaqIA1* allele and the minor allele of two SNPs of the DRD2-coding region which has been related to lower DRD2 expression (Zhang et al., 2007) might uncover this controversial question.

The present cued task-switching paradigm (Barcelo et al., 2000) has proved highly sensitive to cognitive control processes, such as online maintenance and updating of goal-representations facilitated by PFC and striatal DA activity. Moreover, the current results support the hypothesis of an inverted-U function between PFC DA activity, task-switch costs and its neurophysiological correlates. The present study did not assess the potential gender effects of the gene–gene interaction on

contextual updating of mental representation. Since there is evidence for menstrual cycle dependent influences of gonadal steroids on dopamine function (Becker et al., 1982; Becker and Cha, 1989; Dreher et al., 2007), further studies should address the current issue controlling for possible confounding factors such as the menstrual cycle. Despite of the apparent parallelism between behavioral and EEG data across the groups, four mean group values are insufficient for a statistical test of this inverted-U association. In spite of the small sample[2], the present outcomes also provide evidence for the combined role of *COMTVal108/158Met* and *ANKK1TaqIA* phenotypes in the flexible control of human attention, and they could help in improving our understanding of the pharmacological treatment of attentional disorders and related neurological diseases, given the individual variability in drug responsiveness as a consequence of the genotype. Furthermore, our results suggest that a well-known brain signature of contextual information processing (Barcelo et al., 2006), namely the nP3 brain potential, may serve as a trustable endophenotype for the functional activation of the corticostriatal DA system. The task-specific stereotypy disclosed here for this brain response makes it a good candidate to bridge the gap between genetics and behavior.

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[2] "The limitations of conventional F statistics when testing for multiple gene–gene interactions are comparable to those of multiple tests in the brain imaging literature (Friston et al., 2002, 2007 Petterson et al., 1999), and advocate for a progressive adoption of Bayesian inference in genetic studies (Zhang et al., 2011). From this perspective, identical *p* values convey identical level of evidence irrespective of the sample size (Wagenmakes, 2007), and *p* values from conventional F statistics have been shown to overestimate the evidence against the null hypothesis, a tendency that increases with the number of observations. Since *p* value is influenced by both effect size and by sample size, whenever two studies with different sample sizes yield the same *p* value, it follows that the study with the effect size is always largest in the study with the smallest sample size (Bakan, 1966)."

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