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The role of the dopamine transporter DAT1 genotype on the neural correlates of cognitive flexibility

M. Garcia-Garcia,[1,2] F. Barceló,[2,3] I. C. Clemente[1] and C. Escera[1,2]
[1]Institute for Brain, Cognition and Behavior (IR3C), University of Barcelona, Spain
[2]Cognitive Neuroscience Research Group, Department of Psychiatry and Clinical Psychobiology, University of Barcelona, P. Vall d'Hebron 171, 08035 Barcelona, Spain
[3]Clinical Neuropsychology Research Group, University of Balearic Islands, Mallorca, Spain

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Abstract

Cognitive flexibility, the ability to adapt goal-oriented behaviour in response to changing environmental demands, varies widely amongst individuals, yet its underlying neural mechanisms are not fully understood. Neuropharmacological and human clinical studies have suggested a critical role for striatal dopaminergic function mediated by the dopamine transporter (DAT). The present study aimed at revealing the role of the DAT in the individual brain response stereotypy underlying cognitive flexibility. A task-switching protocol was administered to a sample divided according to the presence or absence of the 9-repeat (9R) allele of the DAT1 polymorphism, while registering behavioural and electrophysiological novelty-P3 responses. The absence of the 9R (higher gene expression) is related to less striatal DA availability. Individuals lacking the 9R (9R−) showed specific response time (RT) increases for sensory change and task-set reconfiguration, as well as brain modulations not observed in participants with the 9R allele (9R+), suggesting that task performance of the former group depended on immediate local context. In contrast, individuals displaying high striatal DA showed larger RT costs than 9R− individuals to any sensory change, with no further increase for task-set reconfiguration, and a larger early positive brain response irrespective of the task condition, probably reflecting larger inhibition of any previous interference as well as stronger activation of the current task set. However, the polymorphic groups did not differ in their mean RTs in trials requiring task-set reconfiguration. This distinct stereotypy of cerebral responses reveals different patterns of cognitive control according to the DAT1 gene polymorphism.

Introduction

Cognitive flexibility, the ability to adapt goal-directed behaviour in response to changing environmental demands, is one crucial factor in the executive control of attention, and yet it varies widely amongst individuals. The dopamine (DA) function might mediate such individual differences in the brain mechanisms of cognitive flexibility, as DA receptor binding in the human striatum has been shown to enhance cognitive flexibility by facilitating the updating of new relevant representations in working memory (Frank, 2005; Cools, 2008). Enhanced striatum DA function promotes exploratory and orienting behaviour (i.e. attention orienting towards novel stimuli) and behavioural switching (i.e. novel actions; Kaplan & Oudeyer, 2007). On the other hand, DA depletion by experimental manipulation (Sawaguchi & Goldman-Rakic, 1994) or in clinical conditions such as Parkinson's disease (Lewis *et al.*, 2003) impairs performance on set-shifting tasks.

The DA transporter (DAT) is the most important DA regulator at the human striatum (Sesack *et al.*, 1998) as it mediates DA active reuptake from the synapse (Lewis *et al.*, 2001). A functional variable number of tandem repeat (VNTR) polymorphism was identified in the DAT1 gene with 9- and 10-repeat (9R and 10R) as the most frequent alleles in the population (Vandenbergh *et al.*, 1992). The 10R/10R genotype results in increased DAT expression (Heinz *et al.*, 2000; Fuke *et al.*, 2001; Mill *et al.*, 2002; VanNess *et al.*, 2005; see, however, Jacobsen *et al.*, 2000) and, putatively, decreased synaptic DA tone in cortico-striatal pathways (Wichmann & DeLong, 1996).

In the present study, we explored the role of the DAT1 genotype in the individual differences in cognitive flexibility by examining the influence of the 9R allele in the behavioural and electrophysiological response to a task-cueing protocol inspired by the Wisconsin Card-Sorting Test (WCST; Rubinstein *et al.*, 2001) and adapted for measuring human event-related brain potentials (ERP; Barcelo, 2003). Barcelo *et al.* (2006) have recently demonstrated that auditory cues directing a switch in the mental set to a new task elicit a characteristic electroencephalographic (EEG) response known as the 'novelty-P3' (nP3) complex. This nP3 response accounts for operations of context updating involved in the processing of both sensory novelty (Escera *et al.*, 1998, 2000; Escera & Corral, 2007) and task novelty (Barcelo *et al.*, 2002), as reflected by a late fronto-posterior positivity, which is preceded by an early fronto-central positivity

Correspondence: Dr C. Escera, [2]Cognitive Neuroscience Research Group, Department of Psychiatry, as above.
E-mail: cescera@ub.edu

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associated to mechanisms of task rule reactivation (Barcelo *et al.*, 2007).

Because reduced striatum DA levels have been shown to impair cognitive flexibility (Cools *et al.*, 2001, 2003, 2004, 2006; Lewis *et al.*, 2003; Cools, 2008), individuals genotyped 10R/10R are expected to show a more rigid behaviour resulting in larger task-switch cost and a less effective gating mechanism for context update than their counterparts, both reflected on the putative endophenotypical nP3 brain response.

Materials and methods

Participants

Forty individuals (8 men and 32 women, mean age 22 ± 4.2 years, range 18–29 years) participated in the present study. They were recruited from a wider sample of volunteers and were interviewed according to 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 study (interview, buccal cells extraction and EEG recordings), which was in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the University of Barcelona. All subjects had normal or corrected-to-normal vision and normal audition. After exclusion by diagnostic criteria and obtaining the DAT1 polymorphisms, the participants showing the most frequent genotypes (9R/9R, 9R/10R, 10R/10R; Vandenbergh *et al.*, 1992) were selected for an EEG recording session. Participants genotyped as 10R/10R were assigned to the 9R− group associated with the functional effect of increased DAT expression (Fuke *et al.*, 2001; Mill *et al.*, 2002; VanNess *et al.*, 2005), and participants genotyped as 9R/10R and 9R/9R were included in the 9R+ group. Two participants were excluded from the ERP analyses due to a large amount of artefacts in their EEG recordings. From the remaining 38 individuals, 20 composed the 9R+ group and 18 were included in the 9R− group. Participants from each of the two genetic groups did not differ significantly in age, gender and state or trait anxiety scores (Spielberger *et al.*, 1983).

DNA isolation and genotyping

A functional VNTR polymorphism was identified in the 3′-untranslated region of the DAT1 gene with repeat copy number ranging from 3-to-11, being 9- and 10-repeat (9R and 10R) the most frequent in population (Vandenbergh *et al.*, 1992). The 10R/10R genotype results in increased DAT expression *in vivo* (Heinz *et al.*, 2000; see, however, Jacobsen *et al.*, 2000) and *in vitro* (Fuke *et al.*, 2001; Mill *et al.*, 2002; VanNess *et al.*, 2005). In order to genotype the participants for the DAT1 gene, DNA was first collected with cheek cell swabs and extracted using the Epicentres® BuccalAmp™ DNA Extraction Kit (Epicentre, Madison, WS, USA). Upon isolation of DNA, the 40-bp VNTR polymorphisms for the DAT1 gene (rs#28363170) were obtained for each DNA sample following the procedures described by Sano *et al.* (1993), and modified by amplifying PCR-VNTR using a fluorescently tagged primer. An initial 4 min denaturing at 95°C, 30 cycles of denaturing at 95°C for 30 s, annealing at 68°C for 30 s and extension at 72°C for an additional 90 s performed in the presence of the primers DAT-F 5′ 6-FAM TGTGGTGTAGGGAACGGCCTGAG 3′ and DAT-R 5′ CTTCCTGGAGGTCACGG-CTCAAGG were then followed by a final extension at 72°C for another 10 min. Amplification products were analysed using a capillary electrophoresis on the sequencer ABI Prism® 3730 (Applied Biosystems, Foster City, CA, USA) and through the Fragments Analysis Technique with GeneMapper® Software Version 4.0 (Applied Biosystems). The resulting fragments consist of 280 bp for 5 repetitions, 320 bp for 6, 360 bp for 7, 400 bp for 8, 440 bp for 9, 480 bp for 10, 520 bp for 11 and 600 bp for 13 repetitions.

Behavioural 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 four key cards on top of one choice card, all centred on a screen (Fig. 1). The target stimulus subtended a visual angle of 4º horizontally and 3.5º vertically, and remained on display until a response was given or up to a maximum of 3000 ms. Subjects were instructed to match the choice card with one of the four key cards following two possible task rules (colour or shape). To ensure that all participants could see colours properly, the Test of Ishihara was applied for excluding participants with suspected colour blindness. Before target onset, one out of four tonal cues explicitly informed the subject whether to sort the card according to either the 'colour' (500/1000 Hz) or 'shape' (2000/4000 Hz) rules. 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, Albany, CA, USA). Three trial types were defined in order to dissociate the processing of changes in sensory and task representations. 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

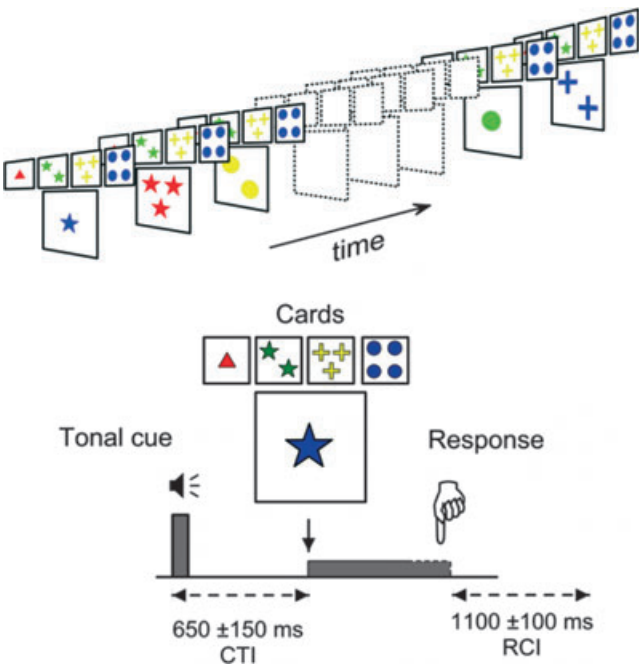

FIG. 1. Stimulus material and experimental design. Each trial consisted of a tonal cue followed by a visual target display with four key cards on top of one choice card. Subjects were instructed to classify targets according to their colour or shape. Before target onset, a tonal cue (500/1000 and 2000/4000 Hz tones) informed whether to classify according to the colour or shape rules. The meaning of the two tones was counterbalanced across subjects. The length of the cue–target interval (CTI) and the response–cue interval (RCI) were jittered.

previous trial. In the 'task-switch' trials both cue and task changed. Responses were made using four keys on a keyboard, mapped onto the four fingers of the dominant hand, in an array corresponding to the layout of the four key cards. The far left button designated the key card on the far left of the display, the far right button designated the key card on the far right, etc. (Fig. 1). All three 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 five times during the instruction period of the practice block, and three more times during the instructions of the experimental block, in order to ensure that each participant had correctly learnt the cue–task association. Whenever the hit rate of the practice block was lower than 75%, an additional practice block was administered to ensure full assimilation of the correct cue–task association prior to the run of experimental block. There was no effect of the DAT1 genotype on the number of practice blocks administered. All the task sets declared in the instructions consisted of four-feature-stimulus to four-forced-response mappings. 'Task set' denotes here, in a broad sense, a set of rules that govern the mapping between sensory inputs and motor responses (Braver *et al.*, 2003). The cue–target interval randomly varied between 650 ± 150 ms, thus minimizing the effects of a constant preparation interval (Rogers & 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 about 1100 ± 100 ms within the trial block.

EEG data acquisition

EEG 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 electrooculographic (EOG) 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 recording session, which lasted about 20 min.

Data processing

ERPs were averaged offline for each trial type (repeat, cue-switch and task-switch), for an epoch of 1400 ms including a pre-stimulus baseline of 200 ms. The first five trials of the block were excluded from analysis. Frequencies above 30 Hz were digitally filtered out from individual EEG epochs prior to ERP 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 ERP averages were 74.4%, 75.1% and 72.7% epochs from the repeat, cue-switch and task-switch conditions, respectively, which did not differ between any of the trial types.

Data analysis

For behavioural analysis, any correct button press within 200–3000 ms after target onset was regarded as a hit, and the mean response time (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 one between-subject factor (Group: 9R+ and 9R−). Pair-wise *post hoc* comparisons were performed to examine any significant difference between conditions.

For the analysis of the auditory brain responses, the mean amplitudes of the following ERP components were computed in the specified latency windows: the early fronto-central positivity from 180 to 220 ms, the late fronto-posterior positivity from 300 to 340 ms, the late negative deflection from 420 to 440 ms. Likewise, the slow fronto-parietal negativity was computed in two latency windows, from 600 to 700 ms (SW1), and from 800 to 900 ms (SW2). All these brain responses were measured at channels F3, F4, Fz, C3, C4, Cz, P3, P4 and Pz. 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 between-subject factor Group (9R+ and 9R−). Pair-wise *post hoc* comparisons were performed across all trial types to examine whether the trial type effect was due to a cue-switch or to a task-switch. The Greenhouse–Geisser correction was applied to the degrees of freedom of the ANOVAs, and the corrected *P*-values were reported whenever was appropriate. Target-locked ERPs were not reported as they did not account for any group-related behavioural cost.

Results

Behavioural results

Both groups showed a decrease of hit rate after a tonal switch (main effect of Trial type: $F_{2,72} = 39.7$, $P < 0.001$), which was due to a decrease in hit rate in the task-switch compared with cue-switch trials ($F_{1,36} = 56.3$, $P < 0.001$). No effect of Group was found for the hit rate. An increase in RTs after a tonal switch (main Trial type effect: $F_{2,72} = 71.6$, $P < 0.001$) was also observed, due to an increase in RT in cue-switch compared with repeat trials ($F_{1,36} = 75.1$, $P < 0.001$). Although the two DAT1 groups did not differ significantly in their mean RT, the most striking behavioural result was the interaction Trial type × Group ($F_{1,36} = 4.4$, $P = 0.033$), which was due to larger RTs in cue-switch trials in the 9R+ relative to the 9R− group ($F_{1,13} = 13.6$, $P = 0.003$). While 9R− individuals experienced a RT delay in task-switch compared with cue-switch trials, the 9R+ ones reached the largest RT increase already in cue-switch trials with no further increase in task-switch trials. No group difference was observed, however, in task-switch trials (Fig. 2).

Electrophysiology

Auditory cues elicited a typical fronto-parietal nP3 consisting of an early fronto-central positivity followed by a late fronto-posterior positivity and a late negative deflection (Fig. 3A). Mean amplitudes of the early fronto-central positivity were substantially larger for the 9R+ group than for the 9R− group, particularly at central and parietal locations. This was supported by a significant Frontality × Group interaction ($F_{2,72} = 5.2$, $P = 0.023$; Fig. 3A and B), there being a main Group effect at central ($F_{1,36} = 6.3$, $P = 0.016$) and parietal ($F_{1,36} = 6.0$, $P = 0.019$; Fig. 3B) locations. However, this brain response was not affected by Trial type. As for the late fronto-posterior positivity, a main effect of Trial type ($F_{2,72} = 13.1$, $P < 0.001$) revealed larger amplitudes after cue-switch compared with repeat trials ($F_{1,36} = 6.7$, $P = 0.013$), and for task-switch compared with cue-switch trials ($F_{1,36} = 7.0$, $P = 0.012$). However, this

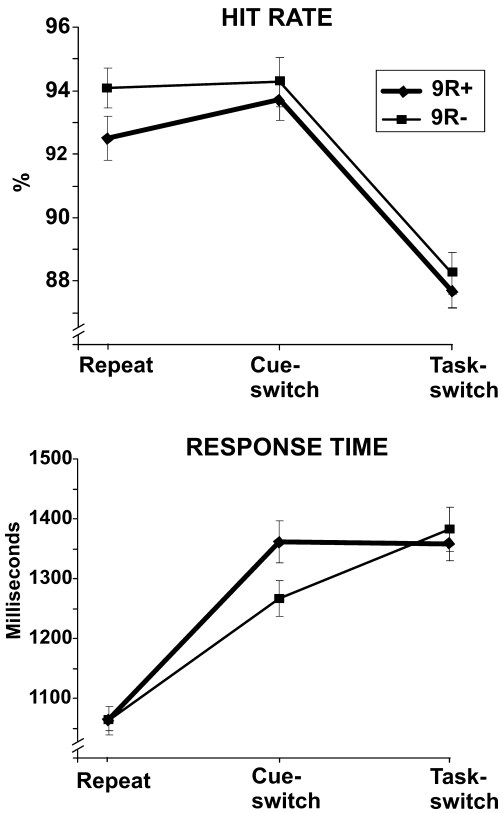

FIG. 2. RTs and hit rates for the 9R+ and 9R− groups across the three trial types. The hit rate was lower in task-switch trials as compared with the other two trial types, with no differences between the groups. The RT plot shows a delay in cue-switch trials for both groups; however, whereas the 9R− group showed larger RT in task-switch as compared with cue-switch trials, the 9R+ group showed similar RT for these two trial types.

late positivity was not affected by the DAT1 polymorphism. The subsequent late negative deflection showed a Trial type × Group interaction ($F_{2,72} = 3.5$, $P = 0.041$), revealing smaller amplitudes in task-switch as compared with cue-switch trials in the 9R− group ($F_{2,34} = 4.5$, $P = 0.028$), while all three trial types elicited similar amplitudes in the 9R+ group (Fig. 4A).

Following the nP3 complex, the late slow fronto-parietal negativity showed a main Trial type effect (SW1: $F_{2,72} = 21.3$, $P < 0.001$; SW2: $F_{2,72} = 15.0$, $P < 0.001$), which was due to an amplitude decrease in cue-switch as compared with repeat trials (SW1: $F_{1,36} = 26.3$, $P < 0.001$; SW2: $F_{1,36} = 22.1$, $P < 0.001$). However, the SW2 reduction was largest in the 9R− than in the 9R+, group as supported by a significant Trial type × Group interaction ($F_{2,72} = 4.3$, $P = 0.017$). The mean amplitude difference between cue-switch minus repeat trials was 3.83 and 2.01 μV for the 9R− and 9R+ groups, respectively (Fig. 4B).

Discussion

A cued task-switching paradigm was used in human subjects with different polymorphic variations for the DAT1, in order to reveal the role of the DAT in human variability in the brain response stereotypy underlying cognitive flexibility. The polymorphic groups showed different patterns of behavioural switch cost: whereas mean RT increased in cue-switch as compared with repeat trials, and in task-switch as compared with cue-switch trials for 9R− individuals, the 9R+ group reached their largest mean RTs in cue-switch trials with no further increase in task-switch trials. The groups differed in their mean RTs during cue-switch but not task-switch trials. This behavioural profile was accompanied by larger early fronto-central positivity at central and parietal scalp regions in 9R+ as compared with the 9R− group. In contrast, task conditions modulated the amplitude of a late negative deflection for 9R− but not for 9R+ individuals.

DAT1 and task-switch cost

Even though both groups showed a RT cost following any change in acoustic stimulation (i.e. a distraction effect; Escera *et al.*, 1998, 2000; Escera & Corral, 2007), larger RT costs were observed between cue-switch and repeat trials for 9R+ than for 9R− individuals, with no further increase in RT costs between cue-switch and task-switch trials.

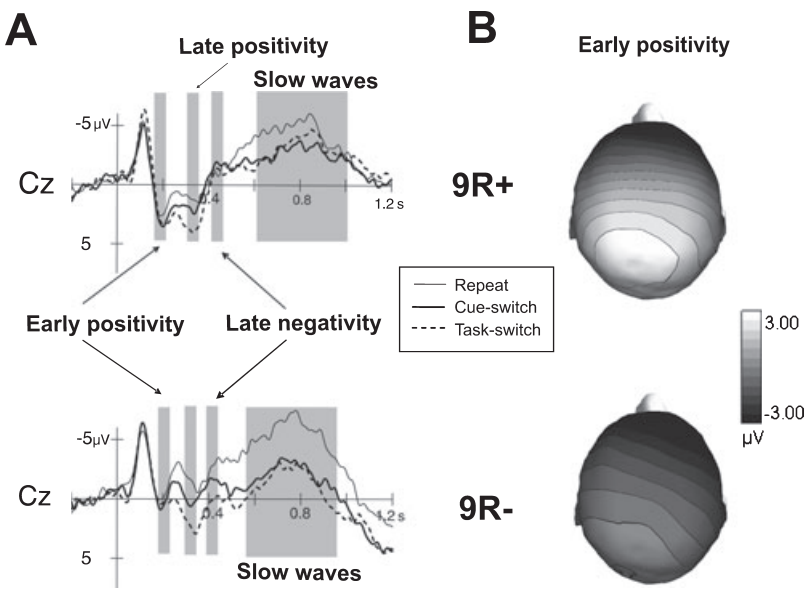

FIG. 3. ERPs elicited by the auditory cues in the three different trial types. (A) Relevant ERP waveforms for both groups across the three trial types have been shadowed at the Cz recording site. Notice the larger early positivity in the 9R+ group relative to the 9R− group. (B) Scalp distribution of the early fronto-central positivity for both groups in repeat trials. This brain potential was larger in the 9R+ than in the 9R− group mostly over central and parietal scalp regions.

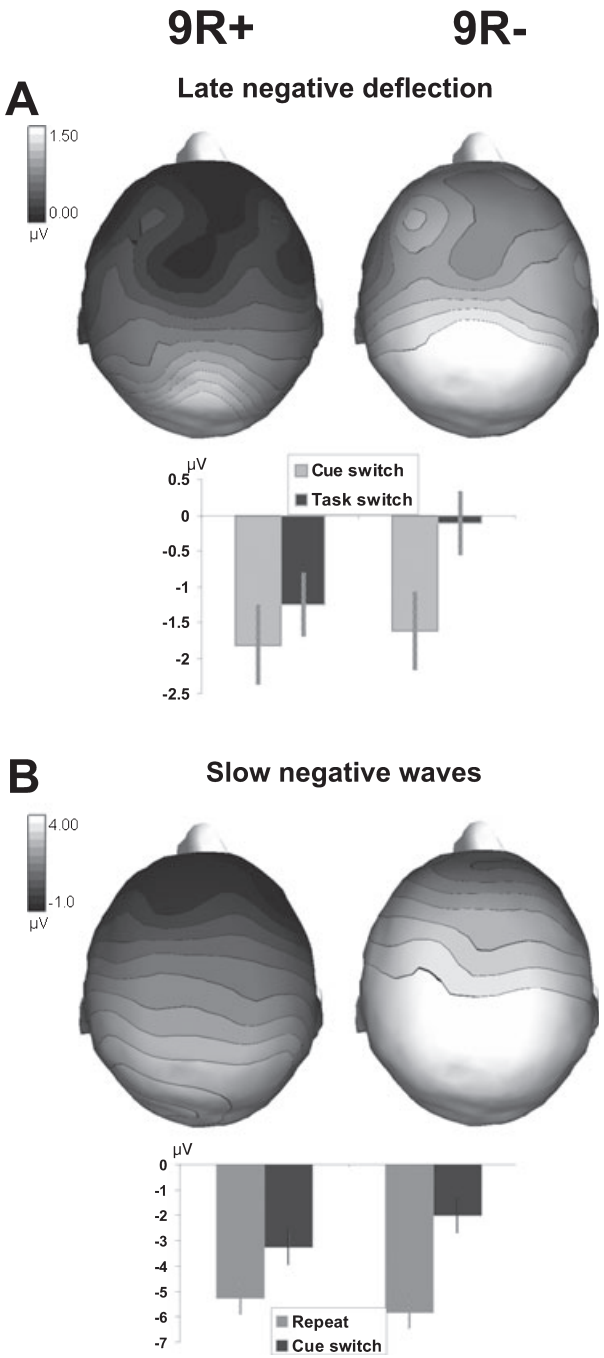

FIG. 4. The frontal negative deflection and the late slow fronto-posterior negativities showed a different modulation by task condition in each of the groups. (A) The scalp distributions of the difference wave obtained by subtracting ERPs of task-switch minus ERPs of cue-switch trials at the late negative deflection. The underlying plot shows the amplitudes in both groups in cue-switch and task-switch trials. The 9R− group displayed an amplitude decrease in the task-switch as compared with the cue-switch condition, not present in the 9R+. (B) The scalp distributions of the differential response obtained by subtracting ERPs of cue-switch minus ERPs of repeat trials at the slow fronto-posterior negativity time range. The underlying plot shows the amplitudes in both groups in the repeat and cue-switch conditions. The 9R− group displayed a stronger amplitude decrease in the cue-switch as compared with the repeat condition than the 9R+.

Conversely, 9R− individuals showed an additional RT cost between cue-switch and task-switch trials (Karayanidis *et al.*, 2003; Fig. 2). The importance of striatal DA in the flexible control of attention (Montague *et al.*, 2004; Kaplan & Oudeyer, 2007) has been revealed by larger task-switch RT costs in conditions of lesser DA display in human striatum (see Cools *et al.*, 2001, 2003, 2006; Cools, 2008) accompanied by a task-switch cost in accuracy. However, in the current study the two groups showed similar mean RTs and hit rates, but nevertheless distinct patterns of switch cost according to their genetic profiles. Larger task-switch costs were predicted for the 9R− group due to their lesser striatal DA display (Cools *et al.*, 2001, 2003; Cools, 2008), although DAT levels alone cannot account for the RT increase observed during task-switching in patients with striatal dysfunction. However, the present results revealed similar mean RTs to task-switch cues in both groups, although 9R− individuals did discriminate between cue-switch and task-switch trials. Instead, the 9R+ group invested similar RTs for processing all cue switches, suggesting a context-independent processing of all auditory changes. 9R+ individuals invested about 100 ms extra for cue-switch trials than the 9R− did. This slower evaluation of a sensory change could be due to an excess of protection against interference (Cools *et al.*, 2001). Our results seem consistent with a relevant functional magnetic resonance imaging study by Cools *et al.* (2004), who reported a significant increase in the blood oxygen level-dependent signal in the striatum in trials involving a change in the visual target without any change in rule. Accordingly, it seems plausible that a reduced activation of the striatum in the 9R− relative to the 9R+ group could lead to the reduced early positivity and the comparatively faster response in the cue-switch trials. Larger DA display in frontostriatal circuits (9R+) might help to protect the current task set in the presence of competing novel sensory or task demands (cf. Cools *et al.*, 2001). Contrary to the 9R+, the 9R− group processed all auditory inputs in a context-dependent fashion, resulting in a comparatively more efficient sorting of cue-switches depending on whether these auditory changes signalled or not the preparatory re-mapping between visual inputs and motor responses (i.e. task-set switching or repetition).

DAT1 and the early positivity of the nP3

Moreover, the 9R+ group showed larger amplitude of the early positivity of the nP3 as compared with the 9R−, irrespective of the task condition, reflecting an effect of the DAT1 genotype on auditory stimulation. In an auditory oddball paradigm, the administration of the D2 receptor antagonist haloperidol resulted in lower amplitudes of a brain response elicited by the auditory target (Kahkonen *et al.*, 2002). Accordingly, this early positivity of the nP3 presumably indicates that a higher DA display allows 9R+ individuals to deploy a stronger reactivation of the task rule, thus avoiding interference from a previous task set (Cools *et al.*, 2001), as suggested by the larger RT to cue-switch observed in 9R+ in comparison to 9R−. Although this is the first study suggesting a direct implication of the striatal DA display in the general mechanism of task-set activation reflected by the early positive component of the nP3, similar DA-regulated fronto-medial positivities (i.e. P2a; Potts *et al.*, 2006) have been proposed to reflect striatum DA signaling, which implements a ‘gating’ mechanism controlling the access of information to neural systems for cognitive control (O’Reilly *et al.*, 1999; Montague *et al.*, 2004; Potts *et al.*, 2006). This is consistent with a recent proposal that the early positive subcomponent of nP3 reflects a general mechanism of task-set activation necessary for the subsequent remapping of stimulus–response associations (Barcelo *et al.*, 2007). Accordingly, larger DA tone in 9R+ individuals facilitates a stronger activation of stimulus–response mappings following every cue. This early positivity failed to distinguish among task conditions. In turn, the late fronto-posterior

positivity discriminated among trial types, although it was not influenced by the DAT1 polymorphism. Hence, this late positivity might be mediated by another neurotransmitter system, such as norepinephrine (Nieuwenhuis *et al.*, 2005), or by the combined action of other DA receptors.

DAT1 and the switch-related negative deflection

The late negative deflection decreased in task-switch as compared with cue-switch trials in the 9R− group, but showed similar amplitudes across all trial types in the 9R+ group. The negative deflection was followed in both groups by a slow fronto-posterior negative wave 600–1000 ms post-cue onset that was larger for repeat than for cue- or task-switch trials. These slow negative waves have been related to improved prediction following repetition (Birbaumer *et al.*, 1990), and hence they were more enhanced after repetition in the 9R− compared with the 9R+ group (Fig. 4). A larger increase of the slow wave in the 9R− group may thus reflect stronger readiness (Walter *et al.*, 1967) whenever there is a sensory match between new and old auditory stimuli, resulting in a more efficient integration of the meaning of a new sound stimulus into the ongoing task context. Moreover, the late negative deflection, which might reflect an early phase of the slow waves, presents larger amplitudes in repeat than switch trials for 9R− as a reflection of more efficient readiness due to the acoustic match between the previous and the current trial. However, a decrease was found in task-switch trials as compared with other trial types, due to the acoustic and semantic mismatch while comparing the current and the preceding trials. In contrast, the late negativity was not modulated in 9R+ individuals by trial type, as they performed task in a context-independent fashion and did not seem to integrate the current cue into the ongoing context. Similar, switch-related late frontal negative deflections have been previously reported in task-cueing paradigms (Mueller *et al.*, 2007), specifically linked to task-switch trials (Brass *et al.*, 2005), and also during preparation for a switch in task after a Go response but not following a No-Go event (Astle *et al.*, 2008), perhaps reflecting interference from the previous task set during motor readjustment (Mueller *et al.*, 2007). These interactions between the trial types and the genotype are reflecting the role of DAT1 polymorphisms on dynamic trial-to-trial adjustments on the cognitive control either to fence off auditory distracters in cue-switch trials, or else to upload the previously-irrelevant-but-currently-relevant S-R mapping in task-switch trials. The 9R− group would experience a weaker activation of mental representations (Cools *et al.*, 2004), as shown by smaller amplitudes of the early positivity, and would display these gating functions at a later stage, through the dissociation of tones signalling either a task-switch or a task-repetition. The current results indicate that this late negative component of the nP3 is mediated by DA and seems to reflect processes needed to integrate new sensory representations to the ongoing task context.

Conclusions and implications

The current study has revealed that the DAT1 gene plays a crucial role in human differences in cognitive flexibility. Performance in a task-cuing protocol was influenced by the presence of the allele 9R (9R+), leading to similar behavioural and electrophysiological responses to all auditory changes regardless of whether these prompted for a repetition or a change in the task rules. This outcome suggests a context-independent processing of such sensory changes, as supported by the similar negative deflection for all trial types in 9R+ individuals in contrast to the 9R− group, showing a modulation by comparing the current trial type with the previous one. Arguably, larger DA display in the striatum, where DAT is mostly expressed (Lewis *et al.*, 2001), would allow 9R+ individuals to deploy a stronger activation of the current task set by avoiding interference from a previous one. In contrast, individuals with a higher gene expression and thus lesser striatum DA availability (9R− group) showed a more context-dependent fashion of cognitive control, sorting cue-switches depending on whether they signalled preparatory control of action within the ongoing task set or as part of a new task set.

Even though the current participants were all healthy volunteers, these results can shed light on the understanding of cognitive disorders or pathologies resulting from striatal dysfunction, for example Parkinson's disease. The rigid behaviour of these patients, as revealed by impairments in the WCST and other task-switching analogues (Cools *et al.*, 2001, 2003, 2004, 2006; Meiran *et al.*, 2004; Cools, 2008), has been attributed to a deficit in the flexible use of abstract task rules (Meiran *et al.*, 2004; Yehene *et al.*, 2008). Likewise, Attention Deficit Hyperactivity Disorder (ADHD) has been related to a poor ability to flexibly adjust behaviour to environmental changes (Nigg & Casey, 2005), and has also been associated to the 10-repeat allele (related to poor striatal DA). The pharmacological treatment of ADHD increases DA levels in the striatum in order to improve attentional functions by increasing the signal-to-noise ratio in target neurons (Volkow *et al.*, 2001). The current results provide strong evidence of the role of the 9R allele in the flexible control of human attention, and could improve our understanding of pharmacological treatment of related disorders or neurological diseases, given individual variability in drug responsiveness as a consequence of the genotype. Furthermore, reported electrophysiological correlates to the switch costs might constitute an endophenotypic marker of such cognitive deficits, and could help to isolate in the near future dysfunction in the human striatum dopaminergic system, even when accompanied by very subtle or no behavioural concomitants.

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Abbreviations

9R, 9-repeat; 10R, 10-repeat; ADHD, Attention Deficit Hyperactivity Disorder; DA, dopamine; DAT, dopamine transporter; EEG, electroencephalogram; EOG, electrooculogram; ERP, event-related brain potential; nP3, novelty-P3; RT, response time; VNTR, variable number of tandem repeats; WCST, Wisconsin Card-Sorting Test.

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